HORMONE
RESEARCH IN
PÆDIATRICS

Milan 2013
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of Paediatric Endocrinology
ESPE-PES-APEG-APPES-ASPAE-JSPE-SLEP
September 19–22, Milan, Italy

9th Joint Meeting of Paediatric Endocrinology

ESPE – PES – APEG – APPES – ASPAE – JSPE – SLEP

Predictive Medicine to Improve the Care of Children

Milan, Italy, September 19–22, 2013

Abstracts

Guest Editor
Franco Chiarelli, Chieti, Italy

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PES: Pediatric Endocine Society
APEG: Australasian Paedriatic Endocrine Group
APPES: Asia Pacific Paedriatic Endocrine Society
ASPAE: African Society for Pediatric and Adolescent Endocrinology
JSPE: Japanese Society for Pediatric Endocrinology
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Plenary Lectures

PL1-1 Stem Cell-derived Islet Cells for Transplantation - PES

Stem cell-derived islet cells for transplantation

Camillo Ricordi
University of Miami, Diabetes Research Center, Miami, USA

Abstract text has not been submitted.

PL2-2 Prevention of Type 1 Diabetes in Children - ESPE

Prevention of type 1 diabetes in children

Mikael Knip
University of Helsinki, Children's Hospital, Helsinki, Finland

Background: There is a need to develop effective measures for the prevention of type 1 diabetes (T1D) since its incidence rate has increased conspicuously over recent decades in most countries, and at the same time the mean age at diagnosis has decreased.
Objective: To present an overview of efforts so far tested for the prevention of T1D.
Methods: The outcomes of intervention studies aimed at preventing clinical T1D or at preserving the exogenous insulin secretion still present in recently diagnosed patients are discussed. The studies can be classified into primary prevention trials aimed at preventing the initiation of the diabetic disease process, secondary prevention trials setting out to prevent the progression of the disease process from beta-cell autoimmunity to incident disease and tertiary prevention trials with the goal to preserve the residual beta-cell function in newly diagnosed children.
Results: The TRIGR study tests the hypothesis whether weaning of high-risk infants to an extensively hydrolyzed formula will reduce the cumulative incidence of T1D later in childhood. It is the only adequately powered primary prevention trial in progress. The disappointing results of two large secondary prevention trials, i.e. ENDIT and DPT-1, have discouraged further large-scale secondary prevention studies, although an emerging interest for pilot trials aimed at secondary prevention can be seen. Over the last decade most efforts have been put into tertiary interventions with the goal to preserve the remaining endogenous insulin secretion in newly diagnosed patients. The results have been variable as some interventions have slowed down the decrease in residual beta-cell function but no therapy has been able to restore the reduced insulin secretion.
Conclusions: We need more detailed knowledge of the disease pathogenesis to develop safe and more effective prevention modalities for T1D. There is still hope as there are new promising modalities in the pipeline.

PL3-3 Programming Effects of Early Life Adversity - APPES

Programming effects of early life adversity

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Traditionally it was believed that common adult diseases such as type 2 diabetes and obesity were caused by genetic risk factors and poor lifestyle. However, in recent years early life events have been identified as a third contributing domain to adult disease. In the mid-1980's Barker and colleagues found that reduced birth size was associated with an increased risk of common diseases in late adult life such as diabetes, metabolic syndrome, hypertension, heart disease and stroke.
Our group and others have identified in children common groups that have developmental programming of adiposity and carbohydrate metabolism. Collectively these studies indicate that as there is deviation away from an optimal fetal and early infant environment the risk factors for type 2 diabetes and metabolic syndrome increase, particularly in those that exhibit rapid weight gain in childhood. For example, infants born SGA small (3% population), LGA (5%), premature (5%), post-term (2-3%) or first born (50-60%) display metabolic disease risk factors such as insulin resistance, increased abdominal adiposity and altered blood pressure and lipid profiles. These periods of programming sensitivity for offspring extend from conception to early infancy. However, persistence of these childhood risk factors into adulthood and the relative contribution of adverse early life events to adult diseases are yet to be determined.
Despite detailed characterization of groups that have undergone metabolic programming the triggers and mechanisms for programming remains to be elucidated. Epigenetic changes in imprinted and other metabolic and growth genes have been proposed as the mechanism for programming based largely upon rodent models of maternal malnutrition. Limited available data in humans suggests that maternal calorie restriction or an unbalanced maternal diet are associated with or alterations in DNA methylation of glucocorticoid, metabolic and growth regulating genes in adult offspring.

PL4-4 Joint Meeting Award Session 1

Rabconnectin-3α is a synaptic protein that controls pubertal onset and reproduction

Juliane Léger[1,2]*; Lukas Huijbregts*[1]*; Brooke Tata*[1]*; Sandrine Jacquier*[1]*; Emmanuelle Genin*[3]*; Sofia Leka*[1]*; Alexandra Durr*[4]*; Jeannette Nardelli*[1]*; Jean-Claude Carel*[2,5]*; Nicolas de Roux*[1,6]
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Background and hypotheses: The association of a GnRH deficiency with a complex neurological phenotype is a rare condition. Here, we describe the cause of a new syndrome observed in 3 brothers, which associated hypogonadotropic hypogonadism, central hypothyroidism, peripheral demyelinating sensorimotor neuropathy, mental retardation, and a profound hypoglycaemia in early childhood progressively transformed to a non-autoimmune insulin-deficient diabetes mellitus.
Methods: A Linkage analysis performed with a single-nucleotide-polymorphism array identified 2 candidate regions, which were then sequenced by high throughput sequencing. A recessive mutation was found in *DMXL2* encoding for rabocnnectin-3α. Functional studies as well as the in-vivo deletion of *Dmxl2* in mouse were then undertaken to delineate the pathological mechanism causing this phenotype.
Results: A homozygous in frame deletion of 15 nucleotides in *DMXL2* leading to the deletion of 5 amino acids was found in the three brothers. Low *DMXL2* mRNA levels were observed in lymphocytes of affected patients indicating that the phenotype was correlated to a gene dosage effect. Rabconnectin-3α was highly co-expressed with synaptic proteins in the external layer of the median eminence, and the cerebellum. In-vivo deletion *of Dmxl2* in neurons caused a severe hypogonadotropic hypogonadism in heterozygous mouse. Finally, we showed that Rabconnectin-3α controlled the glucose-induced insulin release by INS-1 cells.
Conclusions: The disruption of rabconnectin-3α causes a complex neuroendocrine syndrome in humans. Rabconnectin-3α is one of the major hypotha-

lamic proteins controlling the gonadotropic axis at puberty and in adults. This study opens the possibility to delineate the regulation of hypothalamic neuropeptide release as well as the synaptic plasticity leading to puberty.

PL4-5 Joint Meeting Award Session 1

New molecular mechanism for severe familial isolated growth hormone deficiency (IGHD) type I due to mutations in the *RNPC3* gene encoding the minor spliceosome 65KDa protein

Jesús Argente[1,2,3]; Ivon Cuscó[4,5]; Bhupendra Verma[6]; Gabriel A. Martos-Moreno[1,2,3]; Armand Gutiérrez[4,5]; Raquel Flores[4,5]; Ali Oghabian[6]; Julie A. Chowen[1,2,3]; Mikko J. Frilander[6]; Luis A. Pérez-Jurado[4,5]

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Introduction: Recessive mutations in the U4atac snRNA component of the minor spliceosome were recently described in microcephalic osteodysplastic primordial dwarfism type 1 (MOPD1) also called Taybi-Linder syndrome (TALS).
Case study: We present the second human disease caused by mutations in a specific component of the U12-dependent spliceosome. Three prepubertal sisters with severe postnatal growth retardation (height ~-6 SDS) and otherwise normal were studied. GH levels were undetectable after standard stimuli, while prolactin levels were in the low-normal range and the remaining pituitary hormones were normal. Brain MRI revealed anterior hypophysis hypoplasia. The response to GH therapy is excellent.
Results: Mutational and segregation analyses discarded involvement of all known genes of the GH axis. Exome sequencing revealed biallelic mutations in the *RNPC3* gene encoding for the U11/U12-65KDa protein, one of the seven unique protein components in the U11/U12 di-snRNP that mediates the processing of U12-type introns. Mutations are in the second RNA recognition motif (RRM2) that binds to U12 snRNA and is required to bridge between U11 and U12 snRNPs. Significantly reduced cellular levels of U11/U12 di-snRNPs were observed, as well as upregulation of U4atac snRNA and U4atac/U6atac di-snRNA, suggesting a possible compensatory mechanism. RNAseq analyses in blood of probands showed splicing defects of a subset of U12-type introns, indicating partial loss of function consistent with the mild pathological effects. Candidate target RNAs for this tissue-specific phenotype include *ARPC5L*, involved in regulation of actin polymerization and branching of actin networks and expressed in the developing pituitary, and *SPCS2* which participates in cleavage of preprohormones such as ghrelin.
Conclusion: This new molecular mechanism of familial isolated GH deficiency demonstrates the crucial role of the minor spliceosome component in pituitary development and growth regulation.

PL5-6 Novel Therapy for the Metabolic Complications of Obesity - JSPE

Novel therapy for the metabolic complications of obesity through the regulation of the apoptosis inhibitor of macrophages (AIM)

Toru Miyazaki
The University of Tokyo, Molecular Biomedicine for Pathogenesis, Faculty of Medicine, Tokyo, Japan

Obesity induces multiple metabolic and cardiovascular diseases, caused by chronic, low-grade inflammation initially observed in obese adipose tissues. In addition, etiological studies in humans have shown a strong correlation between obesity and autoimmune diseases. Furthermore, obesity is accompanied by fatty liver diseases including non-alcoholic steatohepatitis and hepatocellular carcinoma (HCC). Recently, we found that the apoptosis inhibitor of macrophage (AIM) is involved in multiple steps in the progression of these obesity-associated diseases. AIM is solely produced by tissue macrophages under the regulation by nuclear receptor LXRa, and was initially identified as an apoptosis inhibitor that supports the survival of macrophages against different types of apoptosis-inducing stimuli. As a secreted molecule, AIM is detected in both human and mouse blood at various levels. Under obese conditions, augmentation of blood AIM levels induces vigorous lipolysis in adipose tissue, thereby inducing chronic inflammation followed by diabetes and atherosclerosis. In addition, in blood, AIM binds to IgM pentamers, and this association contributes to production of multiple autoantibodies under obese condition. Contrastively, however, we also found that AIM strongly inhibits liver disease progression. Thus, AIM acts as a key factor that defines the "disease-lineage" following obesity, either to chronic inflammation leading to diabetes, atherosclerosis and autoimmune diseases, or liver diseases. In this presentation, we will discuss about our recent findings and potential applicability of AIM for modern metabolic diseases.

PL6-7 Long-term Follow-up of Patients with Disorders of Sex Development - SLEP

Long-term follow-up of patients with disorders of sex development (DSD)

Berenice B. Mendonca
University of Sao Paulo, Internal medicine, Sao Paulo, Brazil

Background: Patients with DSD present a challenge to professionals who engage in their treatment. The lack of long term follow up data underwrites this dilemma.
Objective: To present an update on DSD long term follow up based on our three decades of experience with these patients.
Methods: The study was mainly retrospective and the patients answered a designed questionnaire containing 152 questions to analyze the impact of the disorder on the patients' social, professional and sexual behavior. We studied 55 patients with the classical form of virilizing CAH and 96 patients with 46,XY DSD grouped in four categories: DSD due to defects in T production (gonadal dysgenesis, LC hypoplasia, 3β-HSD2, 17α-hydroxylase and 17β-HSD3 deficiencies), a 5α-RD2 deficiency group, an androgen insensitivity syndrome (complete and partial forms) group and an undetermined DSD group.
Results: Attribution of female social sex was predominant in both 46,XX and 46,XY DSD groups. Social sex change to male occurred in 18% of 46,XY DSD and in 10% of 46,XX DSD patients. Childhood male or neutral games was the single variable significantly associated with the change of social sex to male in both 46,XY and 46,XX DSD patients registered as females ($p < 0.05$). In 46,XX group, all CAH patients who changed to male sex were improperly treated and had severe virilization. 46,XY DSD due to 5a-RD2 deficiency was the single etiology significantly associated with female to male social sex change. Heterosexual orientation was reported by 94% of the 46,XY DSD patients and by 80% of the 46,XX DSD patients. The patients with 5a-RD2 deficiency had the smallest penile length before and after therapy. However, there was no statistically significant difference in final penile length between sexual satisfied and unsatisfied groups.
Conclusions: Most patients reported high level of satisfaction after treatment, which showed the importance of a multidisciplinary team and psychological support in the treatment of DSD.

PL8-8 The Nature of Nutrition: an Integrative Framework from Animal Adaptation to Human Obesity - APEG

The nature of nutrition: an integrative framework from animal adaptation to human obesity

Stephen J. Simpson[1,2]*; David Raubenheimer*[1,2,3]
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Macronutrients (protein, fats and carbohydrates) are fundamental dietary components, yet the question of what represents a macro-nutritionally balanced diet and how this maintains health and longevity remains unanswered. We have developed a set of state-space models called the Geometric Framework (GF) to capture the multidimensional nature of nutritional requirements, the relative values of foods in relation to these requirements, the behavioural and physiological responses when feeding on diets of varying composition, and the growth and performance consequences of being restricted to particular dietary regimes. We have also derived the necessary theory for defining health and performance in relation to nutrient intake, for describing key nutritional traits and assessing trade-offs between different responses. In the lecture I begin by introducing these models and then show how they have been used to address problems in life-history theory, immunity, ageing, obesity and cardiometabolic health. Along the way I will use examples spanning slime moulds to humans.

PL9-9 New Insights into the Genetic Regulation of Growth - *Dedicated to Rita Levi Montalcini*

New insights into the genetic regulation of growth

Jeffrey Baron
National Institutes of Health, Program on Developmental Endocrinology and Genetics, Bethesda, USA

Background: In the fetus and newborn, body growth is extremely rapid because of rapid cell proliferation in multiple tissues. However, during infancy and childhood, the rate of proliferation declines, causing body growth to slow and eventually cease. Although the decline in cell proliferation occurs concomitantly in multiple organs, it does not appear to be coordinated by changes in hormone levels.
Objective: To explore the mechanisms that allow rapid body growth in infancy but subsequently cause body growth to slow and eventually cease by adulthood.
Results and conclusions: Recent evidence suggests that growth deceleration during juvenile life results from an extensive genetic program which occurs simultaneously in multiple organs and involves the down-regulation of a large set of growth-promoting genes. This developmental genetic program does not appear to be driven simply by time, but rather depends on growth itself. Consequently, if growth is temporarily inhibited, for example by nutritional deficiency, the growth-limiting genetic program slows, thus at least partially retaining growth potential for the future. This putative growth-limiting program is conserved among different mammalian species, but, in larger mammals, the program appears to play out more gradually, allowing for more prolonged growth and therefore greater adult body size. Recent studies suggest that the downregulation of these many growth-promoting genes during juvenile life is orchestrated in part by a transcription factor, E2f3. In early life, E2f3 is expressed at high levels, driving expression of many growth-promoting genes, such as Igf2. With increasing age, E2f3 levels decline, leading to downregulation of these genes. Finally, recent evidence suggests that this growth-limiting control system is defective in some malignancies. For example, in some cancers, E2F3 is overexpressed and appears to drive overexpression of IGF2, likely contributing to the unrestricted growth of cancer cells.

PL10-10 Endocrine Disruptors and Their Effects on Reproductive Health - ASPAE

Endocrine disruptors and their effects on reproductive health

Niels E. Skakkebæk
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Is there a risk that our diet contains substances that can interfere with the endocrine system and thereby act as endocrine disrupting chemicals (EDCs)? Do EDCs used in cosmetics, including sun screens pass the skin barriers and enter the circulation? Can several EDCs act in concert and thereby cause effects, even if the individual chemicals are present in very small concentrations? Should we expect that EDCs contribute to the burden of endocrine diseases in children and adults? Unfortunately, more and more data suggest that the answer to these questions is yes. EDCs include DDT and its metabolites, PCBs, flame retardants and perflourinated compounds and non-persistent EDC-chemicals, e.g. phthalates, bisphenol A and UV-filters in sunscreens. Research through the past 10 years has clearly shown that EDCs can cause harm in wildlife and experimental animals. Particularly their reproductive effects have been studied. A hypothesis that the same chemicals can be harmful for human reproduction is plausible. However, as experimentation with EDCs of course is excluded in humans, final proof that the chemicals cause endocrine diseases in humans is difficult to obtain. There is clear evidence from animal studies that some EDCs, including phthalates, may be more harmful for the developing organism than for adults. We have proposed that fetal exposure to EDCs may contribute to observed adverse trends in human symptoms of testicular maldevelopment, including cryptorchidism, hypospadias, abnormal spermatogenesis and testicular cancer. Ongoing EDC research focuses on interactions between lifestyle factors, genetic factors and EDCs. WHO and UNEP have recently launched a report http://www.unep.org/hazardoussubstances/UNEPsWork/StateoftheScience/tabid/105913/Default.aspx hypothesizing that the widespread occurrence of other endocrine problems, including thyroid diseases and obesity may also be related to EDC's.

Symposia and Meeting Theme Symposia

S1-11 Safety and Appropriateness of GH Treatment in Europe (SAGhE)

SAGhE: project presentation. Investigation plan and objectives

Stefano Cianfarani[1]; Gary Butler[2]; Jean Claude Carel[3]; Peter Clayton[4]; Anita Hokken-Koelega[5]; Marc Maes[6]; Primus Mullis[7]; Roland Pfaffle[8]; Lars Savendahl[9]; Anthony Swerdlow[10]

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Recombinant human growth hormone (rhGH) has been used since 1985. Current indications for rhGH use in children include GH deficiency and an increasing number of conditions where short stature is not primarily due to deficient GH secretion. Whereas the efficacy of rhGH to increase adult height is undisputed in children with "classical GH deficiency", rhGH effectiveness is more uncertain in other indications. GH therapy also implicates issues related to safety. GH use in childhood has been associated with increased long-term risk of cancer, but conflicting and inconclusive data are available. SAGhE is an integrated consortium of pediatric endocrinologists, epidemiologists and biostatisticians, involving 10 partners from 8 EU countries, aimed at collecting and analyzing data from a large EU cohort of subjects treated with rhGH during childhood. The consortium aimed to constitute a large cohort of young adults (approximately 30000), over 18 years of age in 2009, treated with rhGH during childhood in order to evaluate: 1) the efficacy of rhGH therapy in promoting growth; 2) the impact of the growth outcome on quality of life; 3) the long-term mortality and cancer morbidity in comparison with the general population. The study included patients recruited from national or regional registries or from patient databases collected from large regional centers. Patients were included on an intention to treat basis, i.e. including all those who started GH treatment, even if they stopped treatment before completing growth. The inclusion of patients in the database was independent of brand and post-marketing studies organized by Pharmaceutical Companies who market rhGH preparations. The SAGhE consortium aims at integrating the obtained data with the current body of knowledge in the field in order to improve the clinical management and safety of children in the EU. *On behalf of SAGhE project participants.*

S1-12 Safety and Appropriateness of GH Treatment in Europe (SAGhE)

SAGhE efficacy results

Jean-Claude Carel

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Abstract text has not been submitted.

S1-13 Safety and Appropriateness of GH Treatment in Europe (SAGhE)

SAGhE quality of life results

Joël Coste

Hôpital Cochin, Département de Biostatistique, Paris, France

Abstract text has not been submitted.

S1-14 Safety and Appropriateness of GH Treatment in Europe (SAGhE)

SAGhE: preliminary report of all-cause mortality analyses

Lars Sävendahl[1]; Gary Butler[2]; Jean-Claude Carel[3]; Stefano Cianfarani[1,4]; Peter Clayton[5]; Anita Hokken-Koelega[6]; Marc Maes[7]; Primus E Mullis[8]; Anthony Swerdlow[9]; Roland Pfaffle[10]

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Background: Short-term safety of recombinant growth hormone (rGH) treatment is generally considered satisfactory and its evaluation is based on large samples of patients followed in post-marketing databases. In contrast, the long-term safety of rGH treatment has been poorly evaluated. A preliminary analysis of mortality results from France has triggered reactions among patients, health care professionals and authorities which have highlighted the importance of the SAGhE study.
Objective: To study the effects of childhood rGH treatment on long-term mortality and compare this with the general population.
Methods: A large meta-cohort of approximately 25 000 young adults treated with rGH during childhood from several EU countries has been established. Vital status of all patients has been determined using national death registers. Cause of death will be ascertained from national registries and death certificates.
Results: An up-to-date report on the current status of mortality results will be presented.
Conclusions: All partners are more than ever committed to achieve this ambitious but difficult task and to transfer the results of the study to the society.

S1-15 Safety and Appropriateness of GH Treatment in Europe (SAGhE)

SAGhE: preliminary report of cancer incidence and cancer mortality analyses

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Background: Short-term safety of GH treatment has been widely evaluated but information on long-term safety is limited. There have been reports of apparent raised risks of certain cancers in some studies, but based on small numbers and the relation remains unclear.
Objective and hypotheses: To study the effects of childhood GH treatment on long-term cancer incidence and cancer mortality risks.
Methods: A cohort of 25,000 patients treated with GH during childhood in several European countries has been established in the SAGhE project, and data have been collected on site-specific cancer incidence, cancer mortality, and years at-risk in cohort members.
Results: An up-to-date report on the current status of cancer risk evalutation in the SAGhE cohort will be presented.
Conclusions: The SAGhE collaborators will provide large-scale cohort assessment of cancer incidence and cancer mortality risks in relation to GH treatment in Europe.

S1-16 Safety and Appropriateness of GH Treatment in Europe (SAGhE)

Critical appraisal of SAGhE results

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Abstract text has not been submitted.

S2-17 Gender Identity and Behaviour

Gender identity disorders in childhood

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Abstract text has not been submitted.

S2-18 Gender Identity and Behaviour

Brain imaging in gender identity disorders

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Background: According to a prevalent hypothesis about gender dysphoria is that sexually dimorphic features in the brain are shifted from the chromosomal sex.
Objective and hypotheses: The presentation will provide an overview over imaging studies testing this hypothesis.
Methods: The survey includes MRI data of grey and white matter volumes, cortical thickness (Cth), and structural l cerebral connections in adult transsexuals and controls
Results: In male to female transsexuals (MtF) it has been reported that the Cth shows a 'female' pattern, and is described to be greater than in males in the orbito-frontal cortex, the right sensory-motor regions, the parietal and temporal cortex, the precuneus, fusiform, and lingual gyrus. The gray matter volumes (sum of Cth and cortical area) in MtF are reported to be elevated in relation to both male and female controls along right mid line structures, whereas it has been found that the structural connections (in the right anterior cingulum, the right forceps minor, the right superior longitudinal fascicle and the corticospinal tract) are smaller than in control men, but larger than in control women.
FtM show, in contrast, a similar CTh as control females, whereas their structural connections seem greater than in women (and not different from men) in forceps minor, and the right superior longitudinal fascicle, but not in the corticospinal tract. The size of the two latter tracts is found to increase after testosterone treatment. No studies of gray and white matter in FtM have been reported.
Conclusions: In MtF there are signs of impaired masculinization, but also singular features in self-referential areas, congruent with the major discomfort expressed by thse individuals. FtM show signs of enhanced masculinization. In both types of transsexuals, the differences with respect to chromosomal sex are located in the right hemisphere. The available data need, however, to be considerably extended to allow firm conclusions.

S2-19 Gender Identity and Behaviour

Sex steroids and behaviour

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Thousands of experimental studies in non-human species have documented the important role of sex steroids, particularly androgens, in sexual differentiation of the mammalian brain and behaviour. These studies indicate that high concentrations of androgens prenatally or neonatally increase male-typical characteristics, and decrease female-typical characteristics, whereas low concentrations have the opposite effects. Disorders of sex development (DSD) often involve androgen abnormality during early development, and so could produce changes in gender-related behaviour. Indeed, the available evidence shows that early androgen exposure contributes to behavioural differences between the sexes, as well as to differences within each sex. For instance, females with the DSD, congenital adrenal hyperplasia, are exposed to high concentrations of androgens prenatally, and show increased male-typical behaviour, and decreased female-typical behaviour. Convergent evidence that early androgen exposure influences human neurobehavioural development has come from studies of other DSD, as well as from studies relating normal variability in concentrations of testosterone prenatally or neonatally to subsequent gender-related behaviour. Other factors, such as postnatal socialization and processes of gender identification also are important for human gender development, however, and the different types of factors combine in different ways to influence specific gender-related characteristics. Conclusions include: 1. Nature and nurture are not alternative perspectives, but instead work together to shape gender development; 2. Neurobehavioural sexual differentiation is multidimensional, with different dimensions of gendered behaviour subject to different combinations of influences; 3. The brain has a variety of gendered elements, some of which can be male-typical while others are female-typical, and these can change over time.

S3-20 Rare Forms of Diabetes: the Euro-WABB Project

Rare diabetes syndromes, and the development of a Europe-wide registry

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Abstract text has not been submitted.

S3-21 Rare Forms of Diabetes: the Euro-WABB Project

Diagnostic markers and treatment for Wolfram syndrome, a prototype for human endoplasmic reticulum disease

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Background: Wolfram syndrome is a rare autosomal recessive disorder characterized by diabetes mellitus, diabetes insipidus, progressive ataxia, blindness, deafness, and death from neurodegeneration in the third or fourth decade. Currently, no treatment can slow the progression of the disease, thus raising the urgency for developing new therapeutic strategies to combat Wolfram syndrome. Our research group has established an international registry (https://wolframsyndrome.dom.wustl.edu/) and research clinic as well as a fibroblast and iPSC bank of patients with Wolfram syndrome to understand the pathogenesis and natural course of this disorder.
Objective and hypotheses: The endoplasmic reticulum (ER) is a cell compartment taking the center stage for protein production, cell survival, and calcium homeostasis. Our group has discovered that Wolfram syndrome is caused by genetic defects giving rise to a malfunctioning ER. Virtually all organ systems, especially neurons and pancreatic beta cells, can be affected. Wolfram syndrome is devastating - it is extremely difficult to diagnose, requiring consultation by multiple physicians, and at present, and no effective therapies are available. The goal of our research is to identify diagnostic markers, disease progression markers, and treatments for Wolfram syndrome.
Methods: Our research team is utilizing integrated genetics and proteomics to identify the mechanisms, diagnostic markers, disease progression markers, and treatments for Wolfram syndrome.
Results: We have identified disease progression markers and drug targets for Wolfram syndrome. Most of these markers and drug targets are related to ER calcium homeostasis.
Conclusions: We have identified potential diagnostic markers and drug targets for Wolfram syndrome and are currently looking for a drug for a clinical trial.

S3-22 Rare Forms of Diabetes: the Euro-WABB Project

Endocrine abnormalities in the ciliopathies with examples of Bardet-Biedl syndrome and Alström syndrome

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Abstract text has not been submitted.

S4-23 Congenital Hypothyroidism Revisited

Genetics of thyroid development: facts and mysteries

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Development of the thyroid gland is clearly under genetic control. Mutations in the genes identified so far, encoding chiefly transcription factors, cause alterations in thyroid gland organogenesis varying from ectopy to hyoplasia or complete absence of the gland (athyreosis). However many questions remain without a clear answer. How do these transcription factor control organogenesis? Which are their targets? Are other genes involved? The approaches to address these questions will be illustrated.

S4-24 Congenital Hypothyroidism Revisited

Unveiling the genetic landscape of congenital hypothyroidism

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Congenital hypothyroidism (CH) is a highly heterogeneous disorder that can be caused by genetic defects or environmental influences (*e.g.,* iodine excess or deficiency). It is also presumed that interaction of multiple genes, or interaction of genetic and environmental factors cause CH. It has been thought that only a minor subset of CH patients (5-10%) has genetic defects[1]. This classic view is now being challenged by recent mutation screening studies[2-4], which revealed higher mutation-carrying rate (about 20%) than expected. However, none of mutation screening studies conducted to date were 'truly comprehensive' (*i.e.,* screen all causative genes in all enrolled subjects) due to limited sequencing capacities of conventional PCR-based methods.
In 2012, we introduced a next generation sequencer MiSeq (Illumina) that enables us to perform 'truly comprehensive' and ultrafast mutation screening with affordable cost. At present, we have analyzed 216 CH patients using the new screening system, and identified 46 mutation carriers (21%). Mutated genes include *DUOX2* (biallelic) N=27, *TG* N=7, *TSHR* (biallelic) N=5, *PAX8* N=4, *TPO* N=2, and *IGSF1* N=1. Of interest, monoallelic mutations of 'autosomal recessive CH' genes (*i.e., DUOX2, TSHR, TG, etc*) were observed in 37 patients (17%), which is clearly more frequent than in the general Japanese population. Furthermore, 4 out of 37 monoallelic mutation carriers had one or more additional monoallelic mutation(s) in other 'autosomal recessive CH' gene(s). Collectively, out data suggest that non-mendelian and possibly multigenic heritability, as well as classic mendelian forms of CH, accounts for substantial proportion of the pathogenesis of CH.

S4-25 Congenital Hypothyroidism Revisited

Congenital hypothyroidism: the screening programs and epidemiology

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Context: The increased global incidence of CH over the past 20 y may reflect changes in environment, demographics or screening methods.
Literature review: 1) in the USA, iodine intake decreased from 1970 to 1990, yet CH incidence increased from 1990 to 2005 so that other factors must be involved;
2) CH is less frequent in Blacks and may be more frequent in Hispanics and Asians, while dyshormonogenesis is more frequent in Pacific Islanders;
3) screening methods affect CH incidence: in Greece, Italy and the UK, a decrease in thyrotropin (TSH) cut-off on all initial screening samples predictably resulted in increased case detection; in Québec, even a small change on a *second* screening test induced an artefactual increase in CH incidence. The additional cases identified with lower cut-offs predominantly have functional disorders.
Discussion: Whether these cases of mild CH require L-T_4 treatment to attain their full intellectual potential is unknown. The original purpose of CH screening was to identify severe cases in which a benefit was clear (i.e., prevention of intellectual disability). Over the last two decades, this original

paradigm progressively shifted to the detection and treatment of all CH cases, including isolated hyperthyrotropinemias and transient CH, especially among premature or low birth weight newborns. With lowering TSH cut-offs, additional cases are detected and treated but without evidence of benefit of this intervention on intellectual outcome.
This lack of obvious benefit may be the reason why, in the USA, more than a third of children labeled as having CH on the basis of neonatal screening no longer receive treatment after age 4 years.
Conclusion: 1) imaging and long term follow-up are necessary to assess the true incidence rate of CH, its etiology and whether thyroid dysfunction is permanent;
2) if we are to treat patients and not numbers, we need to evaluate whether newborns with mildly elevated TSH benefit from early diagnosis and treatment.

S5-26 Hypoglycaemia in Children with Diabetes - ISPAD/ESPE

Hypoglycaemia: physiological responses in children and adolescents with type 1 diabetes

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Abstract text has not been submitted.

S5-27 Hypoglycaemia in Children with Diabetes - ISPAD/ESPE

The impact of hypoglycaemia on the brain of children with diabetes

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Abstract text has not been submitted.

S5-28 Hypoglycaemia in Children with Diabetes - ISPAD/ESPE

Hypoglycaemia in children and adolescents with diabetes: who is at risk? How to prevent?

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Despite significant improvements in pediatric diabetes care, the risk of severe hypoglycemia is still a major threat for children with type-1 diabetes and their families. Such events are extremely frightening for affected parents, with a long-lasting effect on diabetes management. The definition of hypoglycemia in childhood is not easy: for most events, glucose values are not available. The definition of "help required" is not suitable in young children, while the definition of "coma/convulsion" misses many severe events.
Recent data from the German/Austrian multicenter documentation initiative, DPV, including 65642 patients with a pediatric onset of type-1 diabetes from 238 pediatric centers in Germany and Austria and covering the last 18 years, revealed that the rate of severe hypoglycemia is decreasing during recent years, both for hypos requiring help and for hypos with coma or convulsion. Interestingly, mean HbA1c-levels in pediatric patients have also decreased and the inverse association between HbA1c and severe hypos has become weaker.
However, severe hypos are still more prevalent in young children, a group of patients increasing in numbers. Is has been consistently reported by several studies that severe hypos are significantly less frequent in children on insulin pumps. Among other factors, insulin regimen, type of insulin used, ratio of prandial to basal insulin, dose adjustment, migration background, gender and social status might be relate to the frequency of severe hypos.
Information on patient groups who are at increased risk for severe hypos helps to develop evidence-based strategies to prevent severe hypos in pediatric diabetology, based on changes in insulin therapy, self measurements of blood glucose (SMBG), as well as patient and family education. In the future, continuous glucose monitoring may provide additional safety for patients/families at risk.
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S6-29 Rare Diseases – Epigenetic Mechanisms

Prader-Willi Syndrome

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Abstract text has not been submitted.

S6-30 Rare Diseases – Epigenetic Mechanisms

Silver Russell syndrome: from epigenetic/phenotype correlations to clinical care

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Silver Russell Syndrome (SRS) is characterized by intrauterine and postnatal growth retardation, prominent forehead in young age, relative macrocephaly frequent body asymmetry and severe feeding difficulties in the first years of life. As many of these features are not specific and given the phenotypic variability, the diagnosis remains difficult and the incidence unknown.
Maternal uniparental disomy (mUPD7) for chromosome 7 is identified in 5-10% of the cases and loss of methylation (LOM) at11p15 ICR1 domain (including *IGF-II*) in 50-60%. Some rare 11p15 maternal duplication have also been described. We have very recently characterised in a familial form of SRS, a mutation in CDKN1C, a cell proliferation inhibitor encoded by an imprinted gene in the 11p15 ICR2 domain.
We have diagnosed over 150 SRS patients with proven molecular anomalies, allowing epigenotype-phenotype correlations, long-term follow-up studies and proposal of clinical guidelines. SRS patients with 11p15 ICR1 LOM have a more severe growth restriction at birth than SRS patients with mUPD7 but similar postnatal growth pattern and feeding difficulties.
We also found that ~10% of SRS patients with 11p15 ICR1 LOM have multilocus loss of imprinting at regions other than 11p15 ICR1 and that their methylation pattern at these different imprinted regions may vary according to the studied tissue, revealing a complex mosaic tissue-specific epigenotype for the same patient.
Recent studies have identified *cis*-acting regulatory elements and *trans*-acting factors involved in the regulation of 11p15 imprinting, establishing new potential mechanisms for 11p15 methylation anomalies. SRS, like some other imprinting disorders, is enhanced by assisted reproductive technologies, which highlights the potential role of the environment in imprinting disorders occurrence.

S6-31 Rare Diseases – Epigenetic Mechanisms

Clarification of (epi)genetic mechanisms leading to upd(14)pat and upd(14)mat phenotypes

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Human chromosome 14q32.2 region carries a cluster of imprinted genes including paternally expressed genes such as *DLK1* and *RTL1* and maternally expressed genes such as *MEG3* and *RTL1as* (*RTL1* antisense), together with the germline-derived primary *DLK1-MEG3* intergenic differentially methylated region (IG-DMR) and the postfertilized derived *MEG3*-DMR. Thus, paternal uniparental disomy 14 (upd(14)pat) results in a unique phenotype characterized by facial abnormality, small bell-shaped thorax, abdominal

wall defects, placentomegaly, and polyhydramnios, and maternal uniparental disomy 14 (upd(14)mat) leads to less-characteristic but clinically discernible features including growth failure. To date, we studied 35 patients with upd(14)pat-like phenotype and 12 patients with upd(14)mat-like phenotype, and revealed the following findings: (1) the IG-DMR and the *MEG3*-DMR are methylated and unmethylated after paternal and maternal transmission in the body, respectively; (2) in the placenta, the IG-DMR remains as a DMR, whereas the *MEG3*-DMR is grossly unmethylated irrespective of the parental origin; (2)the hypomethylated IG-DMR and *MEG3*-DMR function as imprinting control centers in the placenta and the body, respectively; (3) the IG-DMR functions hierarchically as an upstream regulator for the methylation pattern of the *MEG3*-DMR in the body, but not in the placenta; (3) heterozygous microdeletions and epimutations (hypermethylations) affecting unmethylated DMR(s) of maternal origin lead to upd(14)pat-phenotype; (4) heterozygous microdeletions and epimutations (hypomethylations) affecting methylated DMR(s) of paternal origin lead to upd(14)mat-like phenotypes; (5) *RTL1as*-encoded *microRNAs* function as a repressor for *RTL1* expression; and (6) excessive *RTL1* expression and decreased *DLK1* and *RTL1* expression are relevant to upd(14)pat-like and upd(14)mat-like phenotypes, respectively.

S7-32 Vitamin D in Health and Disease

Clinical risk factors and impact of vitamin D deficiency in children

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During the past two decades, low vitamin D status has re-emerged as a major paediatric health issue both in developed and in developing countries. First of all, the concern is related to increased prevalence in paediatric age, due mainly to modification in lifestyle, cultural attitudes (less time spent outdoors, use of veils or covering clothes, sunscreen…), air pollution and incorrect diet. In addition, recent studies suggest vitamin D, besides the well-known role in bone mineralization, is linked to several extra-skeletal effects.
Most of the vitamin D requirements are provided by sun exposure. However, sunlight is not risk-free, and vitamin D absorption varies a lot according to different seasons, degree of latitude, time of day, area of skin exposure and skin pigmentation. Natural content of vitamin D in paediatric diet is mostly found in non staple food such as fatty fish, nuts and egg yolk; alternative sources are fortified foods, which however are not very common in Europe.
A major risk for infants is maternal vitamin D deficiency, in particular in dark skinned or veiled pregnant women and in infants breastfed for a long period.
In older children risks of deficiency include long term hospitalizations due to chronic illnesses or patients with skin pathologies. A debated topic is if lower levels of 25(OH)D found in obese children have negative consequences for bone health. Children suffering from various severe intestinal diseases may present vitamin D deficiency due to malabsorption. Interference with the activation of vitamin D may be caused by severe chronic hepatic or renal diseases, or by the chronic use of several drugs.
The supplementation of vitamin D is a subject of active debate among authors. While supplementation is univocally accepted for all children with chronic diseases or other vitamin D-deficiency risk factors, supplementation is still under discussion for healthy children.

S7-33 Vitamin D in Health and Disease

Rickets, past, present and future

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"Nutritional rickets" is a condition with a long history with descriptions present in the ancient Greek and Roman literature. The earliest detailed description was published by the English anatomist Francis Glisson in 1651.
In the 19th and early 20th centuries rickets was prevalent in cities in Northern Europe and the United States with 80% of infants under the age of 2 years at the Infants hospital Boston in 1898 having signs of the condition. The identification of a substance present in cod liver oil and from the action of sunlight on the skin that could heal rickets led to the discovery of vitamin D. Widespread food fortification and supplementation of breast fed infants with vitamin D led to a dramatic reduction in the prevalence of rickets by the mid 20th century.
However there has been a significant resurgence of the condition in recent years in many developed countries and a continuing problem in the tropics. The key to the future prevention of rickets are effective vitamin D supplementation public health programmes of which there are some good examples. Vitamin D supplementation needs to be regarded as an essential component of child health provision similar to immunisation programmes if we are to see an effective eradication of "nutritional rickets".

S7-34 Vitamin D in Health and Disease

Extra-skeletal effects of vitamin D

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Vitamin D sufficiency is important for optimal calcium and phosphate homeostasis as well as bone and muscle function. There are vitamin D receptors in nearly every nucleated cell and many tissues have the capacity to produce the active hormone, 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D (25OHD) the major circulating metabolite, raising the possibility that the vitamin D system facilitates optimal functioning of many other body systems. There is a considerable amount of reasonably consistent evidence from laboratory studies which support the proposal that adequate vitamin D and its metabolites contribute to a variety of useful physiological actions. These include effects in skin to reduce DNA damage from sunlight exposure and photocarcinogenesis; in the immune system, for adequate response to invading pathogens but appropriate tolerance of auto-antigens; to reduce incidence of several types of cancers from carcinogens and subsequent metastatic spread, amongst others. Human studies are considerably more mixed, with some support coming from moderately consistent epidemiological studies showing a relationship between low 25OHD levels or sunlight exposure, and relevant poor health outcomes. Mostly, though, causality is difficult to establish. Randomized controlled trials would help settle these questions, but are difficult to do properly for a variety of reasons and even more difficult to fund. Good data from adequately powered, well-conducted trials set up to test these proposals are very limited to date. Limited large scale trials are in progress, which may help provide guidance on target levels for vitamin D status for non-musculoskeletal outcomes.

S8-35 The Adipose Organ: All Fat Is Not Created Equal

Development of the adipose organ

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The major function of adipose tissue is to store and release energy in form of lipids in the fat cells. The adipose tissue expands by changing its number and its size of the fat cells. Studies of the whole human major omentum suggest that the number of fat cells is most important for this growth. In adult man there is a high turnover of the fat cells, which is increased in obesity and decreased when adipose tissue is composed of few but large fat cells (hypertrophy). In spite of a high fat cell turnover humans keep the number of fat cells constant over time and this number does not change after weight reduction. Also the lipids within the fat cells are turned over at high rates in humans. During the about 10 years of life-span of a fat cell its lipid content is fully renewed more than 6 times in the normal state. However, this turnover is markedly altered in metabolic conditions. In fat cells of obese the lipid storage is increased and the lipid removal is decreased. In familial combined hyperlipidemia (FCHL), a genetic disorder which conveys a very strong risk for developing atherosclerotic cardiovascular disease, both the lipid storage and lipid removal are decreased in the human fat cells. This causes a low turnover of adipocyte lipids and may be a factor behind dyslipidemia of FCHL. Furthermore, combined dyslipidemia in the general population is also associated with low lipid turnover in fat cells. Thus, at least in man, the turnover of fat cells and their lipid content is important for energy homeostasis in rare as well as common disorders.

S8-36 The Adipose Organ: All Fat Is Not Created Equal

Adipose tissue as endocrine organ

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During the progression from the lean to the obese state, adipose tissue undergoes hyperplasia as well as hypertrophy in an attempt to cope with the increased demand for triglyceride storage. This requires a high degree of plasticity at both the cellular and at the tissue level. The vasculature has to adapt to altered requirements for nutrient and oxygen exchange. A decrease in the plasticity of these processes leads to metabolic dysfunction. To maintain a healthy, non-inflamed phenotype, complex regulatory mechanisms are in place to ensure adipocytes and stromal vascular cells efficiently crosstalk to allow adipose tissue to expand upon increased demand for storage of triglycerides. Therefore, we propose a model of stepwise adipose tissue dysfunction that is initiated by rapid expansion of existing adipocytes to accommodate triglycerides during excess caloric intake. This leads very quickly to an acute, and eventually chronic, state of hypoxia in adipose tissue. These changes also affect adipocyte-derived secretory factors, such as adiponectin. Adiponectin promotes insulin sensitivity, decreases inflammation and promotes cell survival. Adiponectin enhances ceramide catabolism and formation of its anti-apoptotic metabolite - sphingosine-1-phosphate (S1P). Additional anti-lipotoxic factors protect the system from the negative impact of excess free fatty acid exposure under different physiological conditions, such as leptin and FGF21. Combined, our observations suggest a novel role of adipocyte-derived factors that have beneficial systemic effects, with sphingolipid metabolism at its core upstream component.
Dysfunction at the level of adipose tissue causes an impairment of lipid deposition in adipose tissue with a resulting increased accumulation of ectopic fat in the liver. The hepatic stellate cell is also challenged under those conditions and critically depends on proper adipokine function to remain in the quiescent state.

S8-37 The Adipose Organ: All Fat Is Not Created Equal

Sex and racial influences on adipose organ function and dysfunction

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Abstract text has not been submitted.

S9-38 The Testis in 3D (Development, Descent, Dysfunction)

Update on testis development

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Background: It is now accepted that fetal and/or early postnatal events play a critical role in determining later health. There is increasing evidence that this applies also to male reproductive development and, in particular, that subtle dysfunction of the masculinization process in early gestation (< 12 weeks) can fundamentally reprogramme development and function of the reproductive system. This emphasizes the central importance of normal testis development from 7-12 weeks' gestation. the evidence for worsening male reproductive health highlights the topicality and importance of this area.
Objective and hypotheses: To show that any abnormality in 'setting up' the fetal testis will result in fetal Leydig cell dysfunction which in turn causes a cascade of changes that can affect downstream development of ALL male reproductive organs. This is termed the 'testicular dysgenesis syndrome (TDS)' hypothesis.
Methods: Observations in males with reproductive disorders, animal models, including xenograft models of human fetal testis development.
Results: In man, as in rodent models, parameters such as sperm count, testis and penis size in adulthood can be traced back to fetal masculinization dysfunction, as can can disorders evident at birth (cryptorchidism, hypospadias). This spotlights importance of (1) gaining better understanding of the pathways that underpin fetal testis development and susceptibility to disruption, and (2) identifying maternal factors (lifestyle, diet, exposures) that might impact on fetal testis development and function, in order that preventive strategies can be introduced. This talk will emphasize the crucial role that rodent, ad especially xenograft, models can play in helping to identify these.
Conclusions: Use of rodent and xenograft models plus clinical studies have reinforced the TDS hypothesis, and have opened up new possibilities for better understanding, diagnosis and prevention and identify how this may impact on wider aspects of male health.

S9-39 The Testis in 3D (Development, Descent, Dysfunction)

Next generation sequencing reveals new genetic factors involved in human testicular development

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Exome sequencing has emerged as a very powerful tool to identify the genetic basis of rare human Mendelian disorders. This approach is particularly attractive to identify new genetic causes of Disorders of Sex Development (DSD) since these conditions are refractory to classic genetic approaches. Analysing DSD patients, particularly with 46,XY complete gonadal dysgenesis and 46,XX ovotesticular and testicular DSD can provide novel mechanistic insights into the specification of the somatic cell lineage of the human gonad and the choice of somatic sex. We have performed exome sequencing on 60 cases of 46,XY and 46,XX DSD with or without somatic anomalies. These included both sporadic and familial forms of the disorder. Sequencing was performed using the Illumina HiSeq2000 to an average coverage of x50 following exome enrichment using the SureSelect Human All Exon 50Mb Kit. Analyses of the datasets revealed novel mutations in genes previously associated with DSD including *NR5A1, CHD7, FGFR1, CYP11A1, DHH, ARX* and *MAP3K1*. In addition we have identified a number of mutations in genes not previously associated with DSD. These included several *SOX* genes as well as independent mutations in the GATA4 interacting factor *FOG2*. *Ex-vivo* assays demonstrated that these mutations resulted in aberrant biological activity of the proteins. Mutations were also identified in the extracellular matrix protein FBLN2 in a familial case of 46,XY complete gonadal dysgenesis. FBLN2 has previously been proposed as a sex-determining gene. Other mutations were identified in cofactors of the NR5A1 protein, MAP Kinase signalling molecules and major proteins involved in histone modification. Using exome sequencing we can identify a major genetic contributor to the DSD phenotype in more than 50% of the cases, demonstrating the power of this approach to understand the genetic basis of DSD and human testicular development.

S9-40 The Testis in 3D (Development, Descent, Dysfunction)

Anti-Müllerian hormone as a marker of paediatric male hypogonadism

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Sertoli cells are the most active cell population in the prepubertal testis. During infancy and childhood, basal gonadotrophin and testosterone levels are usually uninformative. Testicular function can be assessed by measuring markers of Sertoli cell function without the need for stimulation tests. Anti-Müllerian hormone (AMH) is a distinctive serum marker of the prepubertal Sertoli cell, which is high from foetal life until puberty. AMH production is stimulated by FSH and potently inhibited by androgens. Initially used only to distinguish between patients with Persistent Müllerian Duct Syndrome (PMDS) due to AMH gene mutations and those with AMH receptor mutations, AMH diagnostic usefulness has extended to patients with disorders of sex development (DSD) and, more generally, to detect prepubertal male hypogonadism. In boys with nonpalpable gonads, AMH is undetectable in anorchid patients, but detectable in those with abdominal testes. In prepubertal males with foetal- or childhood-onset primary or central hypogonadism affecting the whole testis (Sertoli + Leydig cells), serum AMH is low. Conversely, when hypogonadism

only affects Leydig cells, serum AMH is normal/high. AMH is also normal/high in patients with androgen insensitivity. In patients of pubertal age with central hypogonadism, AMH is low for Tanner stage -reflecting lack of FSH stimulus-, but high for age -reflecting lack of testosterone inhibitory effect. FSH treatment results in serum AMH rise, whereas hCG treatment increases testosterone levels which inhibit AMH production. In summary, serum AMH determination is helpful in assessing gonadal function, without need for stimulation tests, and orientates the aetiological diagnosis of paediatric male hypogonadism. Furthermore, serum AMH is an excellent marker of FSH and androgen action in the testis.

S10-41 Endocrine Tumours in Childhood

SDH mutations and susceptibility to paraganglioma

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Before the 21st century, it was thought that 10% of paraganglioma/ pheochromocytoma (PGL/PCC) were genetically determined, due to germline mutations in the *RET*, *NF1* or *VHL* genes. After the identification of *SDHD*, *SDHC* and *SDHB* as additional susceptibility genes, it became clear that at least a quarter of PGL/PCC was inherited. Today, more than ten PGL/PCC susceptibility genes (*VHL*, *RET*, *NF*1, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *TMEM127*, *MAX*, *KIF1b*, *PHD2*, *HIF2*, *FH* ..) have been discovered, and more than half of the PGL/PCC developed during childhood are genetically determined. Among all these genes, the *SDHx* genes encoding for the mitochondrial complex II or succinate dehydrogenase, caused Hereditary Paraganglioma syndromes (type 1 to 5). Different genome-wide analyses have deeply deciphered the oncogenic role of *SDHx* mutations and clearly demonstrated that the inactivation of succinate dehydrogenase activates both the pseudo-hypoxic pathway, in inhibiting prolyl-hydroxylases, and DNA methylation, in inhibiting 2-oxoglurate-dependent histone and DNA demethylases inducing an epigenetic silencing Those recent data have brought new insights to the genetic counseling of patients affected by PGL/PCC, supported new recommendations for genetic testing as well as for the management of the affected patients and their families and raise the possibility of innovative molecular targeted therapies for *SDHB*-related metastatic PGL/PCC.

S10-42 Endocrine Tumours in Childhood

Genetic origin of pituitary adenomas

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The spectrum of diseases with predisposition to pituitary adenomas has expanded in the last few years. In addition to MEN1 and Carney complex, SDH and possibly DICER1 mutations can also cause a syndrome which involves pituitary adenomas. In addition, a large group of patients have been identified with familial isolated pituitary adenoma (FIPA), where familial pituitary adenomas are not associated disease with other types of tumours. While in the majority of these FIPA families the disease causing mutation is not known, about 20% harbour a germline mutation is the AIP gene.
Familial or simplex paediatric pituitary adenomas occur primarily in association with *MEN1, AIP* and possibly *DICER1* mutations.
Paediatric patients with an *AIP* mutation typically harbour a GH- or mixed GH/prolactin-secreting adenoma leading to gigantism. The tumour is usually an invasive, sparsely granulated adenoma with poor response to somatostatin analogue therapy and prone to pituitary apoplexy. Interestingly, apoplexy may bring, at least temporary, improvement to disease severity. Other types of pituitary adenomas have rarely been described: prolactinomas, corticotrophinomas and non-functioning adenomas.
The disease is autosomal dominant with low penetrance (10-30%), therefore many patients present as simplex cases. The majority of the mutations are truncating mutations and there is loss of heterozygosity in the tumour tissue. No confirmed genotype-phenotype correlation has been described to date.
Genetic screening is suggested from the age of 4 years. Basal clinical assessment and follow-up may lead to early recognition and treatment of previously unrecognised disease as described now in several young patients. Due to the relative resistance to somatostatin analogues, early therapy in paediatric cases may need to involve growth hormone receptor antagonist to rapidly control growth velocity and height.

S10-43 Endocrine Tumours in Childhood

Familial forms of thyroid cancer

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Thyroid carcinomas represent the most common endocrine malignancy. The incidence during childhood ranges from < 1 case/million/year in children < 5 years of age to ~18 cases/million/year in the 15 to 19-year-old age group. The major subtypes of pediatric thyroid cancer are papillary thyroid carcinoma (PTC) in >90% of cases, follicular thyroid carcinoma (FTC) in 5-10%, and medullary thyroid cancer (MTC) in < 5% of cases. A diagnosis of thyroid cancer in a child should always raise concern for an underlying hereditary condition, which can subsequently have medical, reproductive, psychological and/or social consequences for the patient and family. The differentiated thyroid cancers (DTC; encompassing PTC and FTC), however, are rarely associated with a known genetic disorder and are most commonly sporadic cases with no identifiable risk factor(s) for malignancy. Genetic disorders that have been associated with DTC include the *PTEN* Hamartoma Tumor Syndrome, *APC*-associated polyposis disorders, Carney Complex, and Werner Syndrome. In < 5% of cases, there is a clear family history of DTC, and the term familial nonmedullary thyroid cancer (FNMTC) has been used to describe such kindreds with ≥ three first-degree relatives with DTC. The susceptibility gene(s) for FNMTC has not yet been identified. In contrast to DTC, MTC is almost always hereditary when diagnosed during childhood and arises within the clinical context of multiple endocrine neoplasia (MEN) type 2, which is caused by autosomal dominant, activating mutations of the *RET* proto-oncogene. MEN2 genotype-phenotype correlations continue to evolve. In the presymptomatic child with a known *RET* mutation, the most difficult decision remains the age at which to recommend early surgical intervention. The current talk will review our contemporary understanding of the familial forms of thyroid carcinoma and the general approaches to the management of children diagnosed with (or at risk for) a hereditary thyroid neoplasm.

S11-44 Environmental and Genetic Disorders of Puberty

Trends in puberty timing and environmental modifiers

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Much earier puberty is occurring nowadays in children, especially in girls. These worrying changes cannot be attributed to genetic modifications, but must be due to lifestyle changes and/or environmental exposures.
Theoretically, obesity, physical inacitivity, insulin resistance and exposure to endocrine disrupting chemicals in combination with certain susceptability genes may all be involved in the marked changes in pubertal timing that we have observed at the population level. The cross-sectional and longitudinal parts of the COPENHAGEN Puberty study addresses these issues.

S11-45 Environmental and Genetic Disorders of Puberty

Multigenetic control of the onset of puberty

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Age at menarche varies widely between girls, is estimated to be highly heritable and is associated with long-term health outcomes, such as obesity and type 2 diabetes. Genome-wide association studies (GWAS), which genotype hundreds of thousands of common genetic variants located across the entire genome, have been successful in identifying many specific genetic determinants of pubertal timing and these findings have informed the mechanisms that link earlier pubertal timing to increased risks of disease.
In 2010, the ReproGEN international GWAS consortium (Elks, Perry, Sulem

et al. Nat Genet 2010;42:1077-85) identified a total of 32 genetic loci that were highly robustly associated with menarche timing. The locus with the strongest individual effect size was LIN28B, which regulates microRNA processing and represents a mechanism that directly links developmental timing to insulin sensitivity. Notably, there was significant overlap between loci associated with menarche and those associated with body mass index, as had been predicted by analyses of data from twins, and in keeping with recognised associations between infancy and childhood weight gain and pubertal timing, and in turn between pubertal timing and obesity in adult life. Still, these 32 loci together explained only 7%-12% of the estimated heritability in menarche timing.
Future large-scale normal population studies, with larger sample numbers and greater power, will undoubtedly identify many further genes involved in the regulation of pubertal timing. It is anticipated that these findings will also inform the aetiologies of clinical disorders of puberty, due to monogenic, oligogenic and syndromic conditions.

S11-46 Environmental and Genetic Disorders of Puberty

Genetic causes of central precocious puberty

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Gonadotropin-dependent precocious puberty, also known as central precocious puberty (CPP), is clinically defined by the progressive development of secondary sexual characteristics before age 8 years in girls and 9 years in boys. CPP has a striking predominance in girls. It results of the reactivation of the hypothalamus-pituitary gonadal axis, which is clinically characterized by the evidence of pubertal levels of basal or stimulated GnRH gonadotropins with consequent gonadal stimulation. Affected children had premature and progressive sexual development associated with advanced linear growth and bone age. No functional or organic abnormality is detected in the great majority of CPP, suggesting an idiopathic form. Despite the great efforts to establish the genetic component of CPP, few genetic alterations were demonstrated in patients with CPP in the last years. Only isolated mutations in *KISS1* and *KISS1R* genes were associated with rare causes of CPP. More recently, using whole exomic sequencing, we were able to identify a single gene, *MKRN3,* encoding the makorin ring finger protein 3, with loss-of-functions mutations in five out 15 families with CPP. *MKRN3* is an intronless gene located on chromosome 15q11.2, in the Prader-Willi syndrome critical region. This gene is imprinted, with expression only from the paternally inherited allele. The inheritance pattern in families with CPP due to MKRN3 defects was in agreement with the expression of *MKRN3* from the paternally inherited allele only. More recently, we identified several loss-of-function mutations of *MKRN3* gene in patients with apparently sporadic CPP. These finding indicated that MKRN3 deficiency is a frequent genetic cause of familial CPP in humans, establishing definitely the genetic component of this common reproductive condition.

S12-47 Glucocorticoid Effects in Bone and Cartilage Tissues

Mechanisms of glucocorticoid action in bone and cartilage tissues

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Background: Glucocorticoids (GCs) are widely used to treat inflammatory diseases and cancers. A multitude of undesired side effects have been reported in GC-treated patients including decreased linear bone growth. We have previously shown that GCs may trigger undesired chondrocyte apoptosis by activating caspase 8, 9 and 3, along with suppression of the Akt-PI3K signaling pathway and trigger Bax-mediated mitochondrial apoptosis in growth plate chondrocytes causing growth retardation in young mice.
Objective and hypotheses: To further explore the mechanisms of altered chondrocyte activities within growth plate, we have explored a number of pro- and anti-apoptotic proteins.
Methods: Pro- and anti-apoptotic proteins were studied in *ex vivo* cultures of rare human growth plate cartilage, cultured fetal metatarsal bones, and human HCS-2/8 proliferative chondrocytes.
Results: Dexamethasone was found to increase the pro-apoptotic proteins, Bax, Bcl-xS, Bad, and Bak as well as the proteolysis of Bid. In this study, we also have used rare tissue samples of human growth plate cartilage obtained from children undergoing epiphyseal surgery, which showed increased level of pro-apoptotic proteins when exposed to dexamethasone. Interestingly, anti-Bax and anti-Bid small interfering RNA rescued the chondrocytes from undesired dexamethasone-induced apoptosis. Finally, mice lacking Bax were completely protected from dexamethasone-induced bone growth impairment, indicating key role of pro-apoptotic proteins.
Conclusions: Our data suggest that GCs treatment differentially regulates Bcl-2 family member proteins to facilitate mitochondrial apoptosis in proliferative chondrocytes thereby contributing to GC-induced bone growth impairment. Prevention of this imbalance between pro- and anti-apoptotic Bcl-2 family proteins may provide a new potential strategy to minimize adverse effects of GCs on bone growth.

S12-48 Glucocorticoid Effects in Bone and Cartilage Tissues

Clinical management of growth impairment in chronic disease

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Chronic diseases such as inflammatory bowel disease and, particularly Crohn's disease, (CD) can cause growth failure during childhood as well as a reduction in final adult height. The underlying mechanism is multifactorial and includes poor nutrition, chronic inflammation, and the prolonged use of steroids. Despite major advances in the treatment of such conditions, a substantial cohort of children continues to display a deficit in linear growth and may qualify for growth-promoting hormonal therapy. However, currently there is limited evidence to support the use of endocrine therapy directed primarily at improving growth. This review is aimed at summarising the current clinical and experimental evidence for growth impairment in chronic inflammatory disease and discusses the rationale for growth promoting therapy.

S12-49 Glucocorticoid Effects in Bone and Cartilage Tissues

Manifestations, prevention and treatment of osteoporosis in children with glucocorticoid-treated diseases

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Recent studies confirm that systemic glucocorticoid (GC) therapy is associated with an increased risk of bone fragility (osteoporosis) in childhood. For example, children prescribed 4 or more, one week courses of oral steroids have a four-fold increased risk of extremity fractures. Vertebral fractures (VF) have also emerged as an important manifestation of osteoporosis in this setting, occurring in up to 35% of GC-treated children with serious diseases such as leukemia, rheumatic conditions and Duchenne muscular dystrophy. Prospective surveillance studies of GC-treated children with leukemia and rheumatic conditions have shown that most of the VF burden occurs in the first 12 to 24 months of GC exposure, that VF are frequently asymptomatic, and that children with a history of VF (including mild vertebral collapse) are at increased risk for future spine fractures. On the other hand, children with transient bone health threats have the unique potential for vertebral body reshaping, either spontaneously or with bone-specific treatment. Recovery from fracture-induced deformity is growth-dependent, underscoring the importance of timely diagnosis and intervention. Prevention begins with optimization of conservative measures, including physical activity, calcium and vitamin D intake, plus treatment of endocrinopathies and aggressive treatment of the underlying disease using the lowest effective GC dose. These measures may be insufficient to prevent fractures in some, raising the need for bone-specific therapy. Since bone-targeted treatment is typically reserved for children with overt fragility, careful monitoring to avoid advanced osteo-

porosis presentations is paramount. Bisphosphonates are the most commonly prescribed agents in children; however, interest in the use of novel osteoanabolic therapy is mounting given bone histomorphometric observations that GC-associated osteoporosis in children is typically characterized by significant reductions in bone turnover.

S13-50 Why Doesn't Everyone Become Obese: Energy Intake and Expenditure

Neuroendocrine regulation of energy expenditure

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Abstract text has not been submitted.

S13-51 Why Doesn't Everyone Become Obese: Energy Intake and Expenditure

Metabolic effects on neuroregulation of homeostasis in the brain

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Abstract text has not been submitted.

S13-52 Why Doesn't Everyone Become Obese: Energy Intake and Expenditure

Lifestyle interventions for weight loss: principles and pitfalls

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Background: Rising rates of obesity in youth have been associated with increased prevalence of type 2 diabetes and concerns for early development of cardiovascular disease as well as other complications of diabetes. Studies such as the US Diabetes Prevention Program and the Finnish Diabetes Prevention Study have shown that improving unhealthy lifestyle behaviours such as poor diet and low levels of physical activity in adults at high risk for diabetes can prevent diabetes. Other studies have shown that improving lifestyle behaviours in adults with type 2 diabetes can improve some health outcomes such as leading to partial remission of diabetes as was shown in the Action for Health in Diabetes (Look AHEAD) Study. However, efforts to utilize these methods in youth have met with limited or lack of success as was most recently shown by the results of the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study. Clearly, we cannot simply extrapolate results in youth from those in adults and even in adults, there is much that is not known about behavioural intervention. This talk will discuss the current knowledge about the effectiveness of behavioural interventions in adults and youth with type 2 diabetes and look at what has succeeded and what has not in order to highlight further fertile areas for research.
Conclusions: Determining effective behavioural interventions in youth at risk for obesity and diabetes is critical to developing targeted treatments for this population. Further research is required to determine the optimal ways to improve measures of health in youth and adults with diabetes.

S14-53 Autoimmunity in Paediatric Endocrinology

Mechanisms of endocrine autoimmunity in children

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Abstract text has not been submitted.

S14-54 Autoimmunity in Paediatric Endocrinology

The clinical spectrum of APS-1 and beyond

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Autoimmune polyendocrine syndrome type I (APS-1) is a rare autosomal recessive disorder which starts in early childhood and is typically associated with chronic mucocutaneous Candidiasis. Patients with APS-1 develop autoimmunity against endocrine tissues such as the adrenal cortex and the parathyroid glands, and non-endocrine tissues e.g. melanocytes and the liver. The disease is caused by mutations in the autoimmune regulator (AIRE) gene that encodes a 54 kDa protein expressed in thymic medullary epithelial cells instrumental in negative selection of autoreactive T cells.
APS-1 patients display autoantibodies directed against proteins in the affected tissues. These autoantibodies are often predictive for the development of organ failures such as adrenal insufficiency or premature ovarian failure where autoantibodies reactive to 21-hydroxylase and side-chain cleavage enzyme, respectively, can be detected. Using novel proteomic arrays with more than 9000 individual proteins in duplicate we have recently been able to identify a number of novel autoantigens, all of which display strict tissue-specificity. These findings reveal novel and not previously decribed clinical components of APS-1. The usefulness of autoantibody analyses in the clinical management of these patients will be discussed.

S14-55 Autoimmunity in Paediatric Endocrinology

Environmental and epigenetic factors in type 1 diabetes autoimmunity - where are we?

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Type 1 diabetes (T1D) is an autoimmune disease characterized by the destruction of the insulin producing cells in the pancreatic islets. Islet autoimmunity (IA) precedes and is strongly predictive of T1D. The recent rise in T1D incidence, coupled with data suggesting an increasing penetrance of moderate-risk HLA-DR genotypes, suggests that environmental factors are increasingly influential in T1D disease etiology. However, the identification of these potentially modifiable factors has so far been elusive.
Perinatal factors and infant diet exposures, such as age at introduction of cow's milk, cereals/gluten and other solid foods have been inconsistently associated with T1D and IA. Enteroviruses and childhood dietary exposures, including increased cow's milk intake, and decreased vitamin D and omega-3 fatty acid intakes have also been implicated in T1D and IA etiology, although inconsistently. The inconsistencies may be due to the modifying effects of other exposures or genes, as recent investigations of gene-environment and environment-environment interactions suggest.
One of the mechanisms behind observed gene-environment interactions may be via alterations in the epigenome. Epigenetic patterns are flexible enough to respond to environmental stimuli, suggesting that subtle alterations in expression of key genes with subsequent dysregulation of autoimmune activity in response to dietary exposures during development are plausible mechanisms contributing to IA and T1D. Little is known about epigenetics and T1D, although one epigenome-wide association study in monozygotic twins discordant for T1D reported a significant association between differential DNA methylation at 132 CpG sites and T1D, and another explored methylation of the insulin gene promoter. Investigations are needed to explore the hypothesis that the development of IA and T1D is mediated by variation in DNA methylation patterns that are induced by exposure to dietary triggers.

S15-56 Emerging Etiologies of Hypopituitarism

Novel genes involved in hypopituitarism

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Normal hypothalamo-pituitary development is closely related to that of the forebrain, and is dependent upon a complex genetic cascade of transcription factors and signalling molecules that may be either intrinsic or extrinsic to the developing Rathke's pouch. These factors dictate organ commitment, cell differentiation, and cell proliferation within the anterior pituitary. Abnormalities in these processes due to mutations in genes encoding both signalling molecules and transcription factors are associated with congenital hypopituitarism, a spectrum of disorders that includes septo-optic dysplasia (SOD), combined pituitary hormone deficiencies (CPHD), and isolated growth hormone deficiency (IGHD). These include *HESX1*, *LHX3*, *LHX4*, *PROP1*, *POU1F1* and, more recently, *GLI2*, *OTX2*, *SOX3*, *SOX2* and genes implicated in Kallmann syndrome, including *FGF8*, *FGFR1* and *PROKR2*.
Mutations in genes implicated in early pituitary development may be associated with highly variable extra-pituitary phenotypes eg dominant/recessive *HESX1* mutations may be associated with SOD, CPHD and IGHD. *SOX3* duplications and polyalanine expansions have recently been described in association with hypopituitarism and variable mental retardation, whilst *SOX2* mutations are associated with predominantly hypogonadotrophic hypogonadism associated with learning difficulties, oesophageal atresia and eye defects. Mutations in genes that are expressed later during pituitary development, on the other hand, are associated with isolated hypopituitarism eg *PROP1* and *POU1F1*.
To conclude, normal pituitary ontogeny in mouse and human is the result of a carefully orchestrated genetic cascade. To date, genetic mutations account for a small proportion of cases of hypopituitarism in humans. We have recently described a novel CPHD syndrome that is due to a mutation in a gene that is implicated in hypothalamic development, suggesting that genes implicated in hypothalamic development may also be implicated in these disorders.

S15-57 Emerging Etiologies of Hypopituitarism

Oligogenic bases of hypopituitarism

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Abstract text has not been submitted.

S15-58 Emerging Etiologies of Hypopituitarism

Novel mechanism leading to hypopituitarism

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Hypopituitarism is caused by genetic abnormalities, tumor, inflammation, and autoimmunity. The pituitary-specific transcriptional factor-1 (PIT-1, also known as POU1F1), plays a pivotal role in regulating the expressions of growth hormone (GH), prolactin (PRL), and thyroid-stimulating hormone (TSH). It is well known that mutations in PIT-1 gene cause a congenital deficiency in GH, PRL, and TSH. Recently, we have reported a novel 'anti-PIT-1 antibody syndrome' in which 3 adult patients with an acquired combined pituitary hormone disease exhibiting GH, PRL, and TSH deficiencies, were specifically associated with circulating anti-PIT-1 antibodies (JCI 2011, 121 113). Although a presence of anti-PIT-1 antibody indicates autoimmunity to PIT-1, it is unclear that this antibody directly plays a causal role because PIT-1 is a nuclear protein. To clarify the pathogenesis of this syndrome, we determined the epitope of the antibody using a phage display system and examined a presence of PIT-1-reactive T cells by an ELISPOT assay. An epitope screening using phage display revealed that two distinct epitopes, which localize in POU homeo- and transactivation- domain in the PIT-1 protein, were recognized by the antibody. Intriguingly, the ELISPOT assay using isolated lymphocytes from the patient demonstrated a presence of PIT-1-reactive cytotoxic T cells, suggesting that the specific impairment of PIT-1-expressing cells was caused by the cytotoxic T cells. It is hypothesized that immune intolerance to PIT-1 occurred with still unknown mechanisms, thereby provoking the attack of PIT-1-expressing pituitary cells by cytotoxic T cells through recognition of PIT-1 epitopes exposed with HLA on the cell surface. These results indicate that immune tolerance to PIT-1 was impaired not only in B cells but also in T cells in the patient and may explain the pathogensis of 'anti-PIT-1 syndrome'.

S16-59 Hyperandrogenism/PCOS during Adolescence

Obesity and hyperandrogenism

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Obesity in childhood is associated with an increase of steroid hormones including androgens.. Increased androgens are a one major condition in polycystic ovarian syndrome leading to hirsuitism and oligo- or amenorrhea. Furthermore, increased androgens in girls are related to cardiovascular risk factors summarized in the metabolic syndrome and increased intima media thickness, a predictive factor for atherosclerosis.
Hyperandrogenemia in childhood is associated to insulin resistance and visceral adiposity. Adipoctokines and the chronic low grade inflammatory state in visceral adiposity deteriorate insulin sensitivity resulting in hyperinsulinemia. This hyperinsulinemia stimulates the androgen synthesis in ovaries and adrenals via activation of hydroxylase and increased secretion of luteinizing hormone (LH). Additionally, the adipocytokine leptin is involved in the regulation of LHRH, which regulates the secretion of LH. Moreover, the function of cytochrom P450 aromatase in ovarian and adrenals, which transforms androgens to oestradiol, is decreased in obese girls. Insulin resistance leads to decreased production of sex hormone binding globulin in the liver increasing free testosterone levels. Furthermore, androstendione is transformed via 17 b-HSD type 3 to testosterone in omental adipose tissue.
Treatment of choice in hyperandrogenism in obesity is weight loss due to lifestyle intervention. Already a moderate weight loss (stable weight in growing children or decrease of BMI 1-2 kg/m²) is associated with normalization of androgens. Since weight loss led to normalization of steroid hormones including androgens (except DHEAS) these findings point towards a consequence and not a cause of increase androgens in obesity. If weight loss is not achievable, drugs (such as metformin, 5 a reductase inhibitors, (antiandrogens) hormonal contraceptives) are alternatives but not approved in childhood for the indication of hyperandrogenism.

S16-60 Hyperandrogenism/PCOS during Adolescence

A critical assessment of the criteria to diagnose PCOS during adolescence

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Polycystic ovarian syndrome (PCOS) is a lifelong disorder characterized by hyperandrogenism and ovulatory dysfunction, with a wide spectrum of clinical symptoms and signs. Three different sets of diagnostic criteria have been established in order to define this disease in adult women that include clinical/biochemical hyperandrogenism, anovulation/menstrual disturbances and polycystic ovarian morphology. A wide array of phenotypes arises depending in the presence of the different combinations of these criteria. Whether the criteria developed for the diagnosis of PCOS in adult women are useful for adolescents is controversial.
During adolescence, ovarian function has especial characteristics regarding ovulatory function, steroidogenesis and folliculogenesis that may lead to difficulties in differentiating physiologic from pathologic findings. The adult criteria used for the diagnosis of ovulatory dysfunction do not seem applicable for young girls, because an irregular menstrual pattern and a decreased ovulatory rate is a physiologic event during this period of life. Also, a high prevalence of polycystic ovarian morphology (PCOM) may be observed during this period. In addition, PCOM is not clearly associated with hyperandrogenism during this period of life, so PCOM is not a useful criterion to define PCOS in young women. These findings suggest that the key factor to diagnose to PCOS during adolescence is hyperandrogenism, and that the diagnosis cannot be suggested in non-hyperandrogenic girls. (FONDECYT GRANT Nº 1100123)

S16-61 Hyperandrogenism/PCOS during Adolescence

Transition of care in PCOS

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder that often becomes apparent in adolescent girls. Adolescent girls who fulfill the diagnostic criteria for PCOS require ongoing counseling and care. As the girls approach adulthood, transfer of care from pediatric endocrinologists to adult-trained providers is appropriate. The need for ongoing multidisciplinary care attentive to the co-morbidities of PCOS should be discussed long before transition is imminent. Transition involves a progressive planned transfer of care that considers medical, psychosocial, educational and cognitive needs of the young woman. Physicians, patients, and parents should discuss the differing expectations between pediatric and adult care providers. This reconfiguration of the doctor-parent-patient triangular relationship to a doctor-patient dyad relationship often generates anxiety for all. The cosmetic, reproductive, and metabolic consequences of poor adherence with healthy lifestyle habits and medications need to be reviewed. Additional potential hurdles during the process include the adolescent propensity to question advice and incomplete comprehension of the consequences of their choices and actions. The need for them to assume responsibility for almost all aspects of their lives further compounds these considerations. For many young adults, health care is not a priority during this period. Young adult women with PCOS may develop diabetes, obesity, hypertension, sleep apnea, metabolic syndrome, and other co-morbidities associated with PCOS in the absence of timely health care. Thus, for these girls, assistance with negotiating the health care maze during the transition is critical because suboptimal transitions can lead to young women to avoid health care until infertility or co-morbidities associated with PCOS become major health problems. Recognizing that PCOS is a chronic illness encourages healthcare providers and patients to better coordinate the transition process.

S17-62 Noonan Syndrome and Other RAS-opathies

The Ras pathway - a critical signaling pathway in health and disease

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Abstract text has not been submitted.

S17-63 Noonan Syndrome and Other RAS-opathies

Spectrum of mutations in Noonan and other RAS-opathies and their correlation with phenotype

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Background: Noonan syndrome (NS) and NS-related disorders (cardiofaciocutaneous syndrome;CFC, Costello syndrome;CS, and LEOPARD syndrome;LS) share common clinical features characterized by unique facial features, postnatal growth failure, psychomotor retardation, ectodermal abnormalities, congenital heart diseases, chest and skeletal deformities, and delayed puberty. To date, this group of disorders has been known to be caused by the gain of function mutations of at least 11 genes of the Ras-mitogen-activated protein kinase pathway. Therefore, NS and NS-related disorders are collectively called RASopathies.
Objective and hypotheses: The study was undertaken to investigate the mutation spectrum and their correlation with the phenotype in Noonan syndrome (NS) and NS-related disorders.
Methods: Clinical characteristics and genotypes of 10 previously known and two candidate genes, *SPRY1-4* and *SPRED1*, were investigated in 109 patients with NS, 21 with CFC, 8 with CS, and 5 with LS.
Results: PTPN11 (46.8%), SOS1 (15.6%), RAF1 (7.3%), KRAS (2.8%), and BRAF (1.9%) mutations were identified in NS; BRAF (52.4%), SHOC2 (23.8%), and MEK1 (9.5%) mutations in CFC; and HRAS and PTPN11 mutations in CS and LS, respectively. No mutation was identified in 24.6% of NS. Functional characterizations of two RAF1 novel variants and one SOS1 variant demonstrated enhanced the activity of Ras-MAPK pathway. Normal stature was frequently observed in individuals with SOS1 mutations, hypertrophic cardiomyopathy in RAF1 & HRAS, pulmonic stenosis in SOS1 and developmental delay in RAF1, BRAF or SHOC2 mutations.
Conclusions: Characterizing genotype-phenotype correlations, our study highlights the role of molecular genetic testing in the process of differential diagnosis of NS and NS-related disorders. In this presentation, the constellation of overlapping clinical features of RASopathies will be described from a genotypic as well as differential diagnostic and managerial point of views.

S17-64 Noonan Syndrome and Other RAS-opathies

Noonan's syndrome: clinical features and management

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Abstract text has not been submitted.

S18-65 Biochemical and Molecular Bases of Diabetic Complications - SIRP/ISPR

Biochemical mechanisms of diabetic angiopathy

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Oxidative stress plays a key role in the development of diabetes complications. The experimental data discussed in the lecture will show how the metabolic abnormalities of diabetes cause mitochondrial superoxide overproduction.
This increased superoxide production is the central and major mediator of diabetes tissue damage, causing the activation of five pathways involved in the pathogenesis of complications: polyol pathway flux, increased formation of advanced glycation end-products (AGEs), increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase C (PKC) isoforms, and overactivity of the hexosamine pathway. It also directly inactivates two critical antiatherosclerotic enzymes, eNOS and prostacyclin synthase. Through these pathways, increased intracellular ROS cause defective angiogenesis in response to ischemia, activate a number of pro-inflammatory pathways, and cause long-lasting epigenetic changes which drive persistent expression of proinflammatory genes after glycemia is normalized ('hyperglycemic memory'). New therapeutic approaches will be also discussed.

S18-66 Biochemical and Molecular Bases of Diabetic Complications - SIRP/ISPR

Molecular machinery of diabetic vascular disease

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Abstract text has not been submitted.

Clinical outcomes of diabetic angiopathy in children and adolescents

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Diabetic angiopathy causes blindness due to retinopathy, renal failure due to nephropathy, unexplained death due to autonomic neuropathy. Each complication has significance for mortality as well as adversely affecting quality of life. The child and family with diabetes are readily aware of these severe outcomes.

Visual loss develops following progression of background retinopathy to proliferative retinopathy. Severity of retinopathy also associates with overall survival. Already well established is the link of albumin excretion with end-stage renal disease and increased mortality. In the Sydney Paediatric Study we have used standardised computer programs to measure retinal vasculature geometry: vascular calibres, tortuosity and branching angles which predict retinopathy and early elevation of albumin excretion.

Large vessel disease and dysfunction may also be developing during childhood and adolescence, as measured by endothelial dysfunction, intima media thickness and cardiac stroke volume. During adolescence arterial elasticity actually increases and is greater with obesity but age-related reduction occurs earlier than for those without diabetes. Puberty itself seems to be an accelerator for complications development especially following attenuation of risk during the prepubertal years of diabetes. Impaired insulin action during puberty is well documented but is likely worsened by accompanying weight gain. When the autonomic nervous system is assessed, the heart rate is increased and heart rate variation is reduced in association with worse metabolic control and insulin resistance.

In 2013, improved clinical outcomes can be expected with better metabolic control and attention to identified risk factors, including weight gain. This is evidenced by 30 year duration outcomes from DCCT/EDIC and other longitudinal studies. Adolescence remains a challenging time for all, and retention in the health care system is essential for good outcomes.

New Perspectives

NP1-68 Imaging in Paediatric Endocrinology

Advances in neuroimaging of pituitary disorders

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Conventional Magnetic Resonance Imaging (MRI) represents the examination method of choice for evaluating the hypothalamic-pituitary axis due to its ability to provide strongly contrasted high-resolution, multiplanar and spatial images.
Beyond anatomy based imaging, advanced MRI techniques such as Diffusion-Weighted Imaging (DWI) and Magnetic Resonance Spectroscopy (MRS), may be helpful in particular cases, as they provide additional physiological and metabolic information.
The correct interpretation of MRI scans requires a detailed knowledge of the normal features of the pediatric pituitary gland and of its dynamic changes in size and shape throughout life, depending on age and sex.
Furthermore, the association of extrasellar findings, accurately defined by MRI, can be extremely helpful for a better definition of several dysfunctional states related to the hypothalamic pituitary axis.
This work begins with some background information regarding normal evolution and MRI appearance of the hypothalamic pituitary region. Then, the most relevant neuroradiological findings related to hypopituitarism, central diabetes insipidus and precocious puberty are described. Finally the most relevant pituitary tumors including adenomas, craniopharyngiomas and germinomas will be discussed, with emphasis on their differential diagnosis.

NP1-69 Imaging in Paediatric Endocrinology

Functional imaging of the pancreas in children

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Congenital hyperinsulinism (HI) is an inappropriate insulin secretion by the pancreatic β-cells secondary to various genetic disorders, with two main clinically indistinguishable histopathological lesions: diffuse and focal.
The differenciation between focal and diffuse HI and the correct pre operative localisation of focal HI are very helpful for clinicians. Focal HI may be definitively cured when the partial pancreatectomy removes the whole lesion. By contrast, severe diffuse forms require a subtotal pancreatectomy (with a long term outcome characterised by a high risk of diabetes) when medical and dietary therapies are ineffective to maintain normoglycemia. Positron Emission Tomography (PET) with fluorine-18 dihydroxyphenylalanin (FDOPA) has been shown as an excellent tool to differenciate focal from diffuse HI and to precisely localise the focal forms. In this respect, the association of PET with contrast enhanced CT (PET/ceCT) in the same examination gives anatomical and vascular landmarks, which is a prerequisite for surgical planning. FDOPA enters the cells through the large amino acide transporter 2, is then converted by aminoacid decarboxylase to dopamine and transported into storage granules by the vesicular monoamine transporter, mechanism characteristic of neuroendocrine cells, including the cells of the pancreatic islets.
FDOPA PET/CT may be considered the first line imaging method in the diagnosis and localisation of focal HI with sensitiviity reported to be 89% and specificity 98% in a meta-analysis recently published (Treglia et al. Pediatr Radiology, 2012).
However, the technique has some limitations: possible false-negative in case of small size of a focal lesion, extensive focal lesion mimicking diffuse disease, location of the lesion near organs with high physiological FDOPA uptake ...
Illustrative clinical cases will be presented as well as the perspective of new PET radiopharmaceuticals, for difficult cases or atypical forms.

NP2-70 Genome Sequencing Promise in Paediatric Endocrinology

The impact of next generation sequencing on paediatric endocrine research

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Next generation sequencing (NGS) methods are now routinely being applied for gene discovery in monogenic disorders. Whole exome sequencing has revealed a bioinactive ACTH molecule, discovered an imprinted gene causal for precocious puberty and identified a dominant negative thyroid hormone receptor to name but a few. Recent advances in the cost effectiveness of NGS have led to its progressively wider implementation in both research and clinical settings. Despite the bewildering amount of data it produces the technique is now being utilised to understand alterations in the transcriptome and the epigenome and to unveil genetic interactions underlying oligogenic disease. The discoveries made using these techniques will ultimately translate into the clinic for timely and cost-effective diagnosis and management of endocrine disease.

NP2-71 Genome Sequencing Promise in Paediatric Endocrinology

Application of genome-wide association studies to childhood diseases

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Genetic factors exerting their effects on metabolism early on in life can in turn strongly dictate health outcomes later on in adulthood, such as influencing the risk of presenting with obesity and type 2 diabetes. In addition, we have reasoned that distillation of the genetic component to such diseases should be easier in children, where environmental exposure and impact has been for a relatively short period of their lifetime.
The Children's Hospital of Philadelphia uses genome wide SNP genotyping platforms and high throughput sequencing technologies. To date, we have genome wide genotyped in excess of 100,000 subjects, allowing us to investigate the genetic component of various pediatric traits based on anonymized medical record information.
It has been reported that reduced birth weight and childhood obesity are both associated with an increased risk of type 2 diabetes later in life. We have made progress in identifying genetic variants that correlate with both these traits and indeed the same alleles turn out to be also associated with type 2 diabetes. We have made these discoveries not only working solely with our own database but also working in a meta-analysis setting, primarily within the Early Growth Genetics (EGG) consortium.
As our cohort mirrors the population structure of Philadelphia, our genetic database contains information on multiple ethnicities. Indeed, studying populations of different ancestries allows us to globally identify and understand the genetic and environmental factors associated with metabolic traits. Variants found in populations of more than one ancestry may represent more universally important genes and pathways for subsequent diagnosis, prevention and treatment of metabolic traits and their complications.

Controversies in Paediatric Endocrinology

CPE1-72/73 Diagnosis and Treatment of Early Puberty

Pros and cons of treatment of early (but not precocious) puberty in girls

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The treatment of early (but not precocious) puberty is controversial. The increasing importance of this issue is based on the recently proposed diminished age limit for normal pubertal onset in girls which would lead to corresponding changes in the definition for precocious puberty. If one considers the age cutoff for precocious puberty to be below the traditional cutoff of 8 years, then a longer window exists for development of secondary sexual characteristics to be classified as "early" as opposed to precocious puberty. In this controversies session, Dr. Palmert will review the literature and present a case **against** using Gonadotropin Releasing Hormone (GnRH) analogs while Dr. Ghizzoni will review the literature and present a case **for** using Gonadotropin Releasing Hormone (GnRH) analogs, to treat girls with early puberty. Because data to inform this therapeutic decision are limited, an important goal of speakers' presentations will be to set the stage for active discussion among the session attendees. Dr. Palmert's discussion against therapy, Dr. Ghizzoni's arguments in favor of intervention, and input from the participants will all be used to inform clinical practice related to early pubertal development.

CPE2-74 Idiopathic Short Stature: To Treat or Not To Treat?

GH for ISS: a decade of safety and efficacy post-FDA-approval

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Background: The use of GH in children with ISS has been approved in the United States and other countries for over a decade; however, it is not yet officially approved in Europe, in spite of extensive experience for its safety and efficacy.
Objective: To demonstrate the rationale for the use of GH in ISS based on the best available evidence
Methods: Analysis of multiple controlled trials and registry data.
Results: Multiple randomized controlled trials lasting up to seven years have compared GH to placebo or various dosing regimens and demonstrated statistically and clinically significant improvements in height velocity, as well as final height. Some studies also suggested improvements in the psychological well being of short children treated with GH.

The dose of GH in ISS children has been approved in the US up to 67 mcg/kg/day. Appropriate use of GH leads to increases final height about 1 SD or approximately 7.5 cm (3 inches). The optimization of GH therapy in ISS (in terms of efficacy, cost effectiveness, and theoretical safety) has been explored in randomized trials of IGF-based dosing and was shown to be improved when the attained IGF-I SDS was between zero and one. Data from multiple commercial registries analyzing tens of thousands of ISS patients largely confirm the auxological benefits of treatment.
Based on multiple sources ranging from clinical trials, registries, and long-term observational databases, the safety of GH therapy in ISS is considered to be as good or better than in GHD patients. Based on all of this information, a consensus for the use of GH in ISS has been achieved through an international workshop sponsored by the GRS, ESPE, and PES and endorsed the judicious use of GH in appropriate patients with well-established ISS.
Conclusions: Extensive long-term experience from controlled trials and registries as well as an international consensus supports the use of growth hormone in appropriately selected children with ISS.

CPE2-75 Idiopathic Short Stature: To Treat or Not To Treat?

Idiopathic short stature: still an enigma for therapy and response

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Background: As the availability of recombinant hGH became established, it was inevitable that idiopathic short stature (ISS) would become a clinical target for its use. Objective and hypothesis: Based on RCTs with hGH using untreated or placebo-controlled groups for comparison significant differences in height velocity, delta height SDS and adult height were demonstrated leading to FDA approval in 2003.
Method: Since then treatment of ISS with hGH has been spectacularly unimpressive.
Results: Submissions to the EMA have failed. hGH therapy has been largely ineffective in producing the generally accepted year 1 response of delta height SDS > 0.5 with reports ranging from 30% to 50% of subjects being unresponsive. In a recent post-marketing Pharma study (abstract at this meeting) the mean delta height SDS in 68 short ISS children with peak GH >10 ng/nl was 0.44 and the non-response rate 62%. Children with short parents and without bone age delay respond particularly poorly. However the perception of increased childhood growth leading to social and professional advantage is now widely held, particularly in emerging economies.
Conclusion: Growth hormone treatment of normal short children is not the answer. This therapy remains experimental and generally unrecommended.

CPE3-76 Detection and Treatment of Congenital Subclinical Hypothyroidism

The benefits of screening for mild forms of congenital hypothyroidism

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The worldwide introduction of progressively lower TSH cutoff values over the last two decades, has resulted in the identification of an increasing number of patients with subclinical hypothyroidism. Most of these cases have a thyroid gland *in situ*, not systematically associated with a known underlying thyroid disease, with only a very small number displaying thyroid dysgenesis. Only a few studies have described the natural course of CH in these children or have addressed the issue of whether subsequent neurodevelopment and long-term metabolic or cardiovascular morbidity can be influenced by a slightly high neonatal TSH levels. It remains a matter of debate whether these children should be treated or monitored. Little is known about etiology and long-term outcome, but about 30% of these patients present a transient form of CH by the age of three years. However, they frequently have a thyroid dysfunction (subclinical hypothyroidism or overt CH), the progression of which remains difficult to predict. A re-evaluation is warranted, to prevent unnecessary long-term treatment. However, it remains unclear how best to monitor these patients, given that many are lost to long-term follow-up, particularly if untreated. The quality of care should be improved by long-term clinical

follow-up studies, which may detect the recurrence of hypothyroidism, which is particularly crucial during childhood, puberty or pregnancy.
Partial defects in genes known to be associated with mild forms of CH, such as those causing partial iodine organification defects (Pendrin, DUOX2 and A2) or TSH resistance, have been documented in a minority of cases, even in transient SH. Other unknown molecular or environmental mechanisms may account for most of these cases. Further studies are required to elucidate the mechanisms of thyroid dysfunction in these patients.
Current screening and appropriate monitoring strategies should enable us to improve our understanding of mild forms of CH and its management.

CPE3-77 Detection and Treatment of Congenital Subclinical Hypothyroidism

Screening for subclinical hypothyroidism: the burden of global over treatment

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Abstract text has not been submitted.

CPE4-78 Fertility Preservation in Pre-Pubertal Children

Fertility preservation in 47,XXY: from childhood to adulthood

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Klinefelter syndrome is the most frequent genetic cause of male infertility. In azoospermic men presenting in fertility clinics, about 1 out of 10 is diagnosed with this syndrome Furthermore, in adulthood, infertility is one of the main reasons to diagnose a Klinefelter syndrome.
Diagnosing Klinefelter's syndrome during childhood is rather occasional: it is estimated that only about 10% of boys with Klinefelter syndrome are diagnosed because of either micropenis, cryptorchidism, growth disorders, gynaecomastia, delayed virilisation, psychological or behavioural problems.
While before puberty their testes seem normal from a histological viewpoint, during puberty the number of spermatogonia is declining and their differentiation is hampered. Gradually, fibrosis and hyalinisation of the seminiferous tubules and the peritubular environment is occurring although focally normally preserved seminiferous tubules may be observed.
In 40 to 50% of adult Klinefelter patients facing infertility, focal spermatogenesis is present and eventually testicular spermatozoa may be surgically recovered to perform intracytoplasmic sperm injection.
Because at puberty, an early wave of active spermatogenesis followed by a rapid loss of spermatogonial stem cells has been described, it is tempting to try to preserve spermatozoa during puberty in patients in which an early diagnosis was made.
However, so far this strategy seems not successful and therefore, in analogy with young cancer patients, testicular stem cell preservation may be a strategy to preserve fertility in Klinefelter boys.
Because of the deterioration of the stem cell niche in the testis in these patients, spermatogonial stem cell transplantation will not be possible. Therefore, developing an in-vitro culture is mandatory. Preliminar data show that in about half of prepubertal or peripubertal Klinefelter boys eventually spermatogonial stem cells can be recovered.

CPE4-79 Fertility Preservation in Pre-Pubertal Children

Fertility after childhood cancer treatment - indications for fertility preservation

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Background: Very high risk to infertility is associated to local or total body irradiation and high-dose chemotherapy. For boys the depletion of spermatogonia pool can occur at any age. If spermatogonial stem cells survive, there is a possibility for spermatogenetic recovery. Testosterone production is generally preserved. Since the female gamete pool is fixed at birth ovarian failure or premature menopause will arise from any cytotoxic insult which either depletes the oocyte pool or hastens its physiological decline. Progressively lower doses are required to produce ovarian failure with increasing age. Premature menopause is characterized by parallel loss of sex steroid hormone production and infertility.
Objective: Indications for fertility preservation in children
Conclusion: All males who are physically mature enough to produce sperm should be offered sperm cryopreservation. If the testicular volume is >6-8 ml, there is a reasonable probability of sperm in an ejaculate. If the boy is unable to produce an ejaculate, alternative methods like vibrator stimulation could be offered. Boys, who are facing oncological treatments associated with a very high risk of infertility, could be offered the experimental procedure of testicular biopsy and cryopreservation of spermatogonia. At present, there are no methods to ensure fertility after such procedures, thus research is warranted. Menstruating girls, mature enough to give informed consent, facing cancer therapy with very high risk of infertility and therapy can be delayed 1- 2 weeks, can be offered ovarian hyperstimulation and cryopreservation of oocytes. The pre-pubertal girls and older girls, who cannot benefit from oocyte cryopreservation, can be offered the experimental procedure of ovarian cortical tissue cryopreservation. At present, healthy children have been born after re-transplantation of adult ovarian tissue. Cancer contamination in the cryopreserved tissue is a contraindication for re-transplantation.

Joint Meeting Working Groups

WG1-80 Bone and Growth Plate (BGP)

Genetic changes affecting growth plate cartilage

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Longitudinal bone growth occurs at the growth plate by endochondral ossification. Within the growth plate, chondrocyte proliferation, hypertrophy and cartilage matrix secretion result in chonodrogenesis. The newly formed cartilage is invaded by blood vessels and bone cells that remodel the newly formed cartilage into bone tissue. This process of longitudinal bone growth is governed by a complex network of paracrine factors that control chondrocyte proliferation and differentiation. Genetic changes in the paracrine regulation of the growth plate cause severe skeletal growth disorders and skeletal dysplasia. More recently, genome wide association studies of normal height variation suggests that common variants in several of these genes also are responsible for normal height variation. This presentation provides an overview of the paracrine signals that regulate longitudinal bone growth, their interactions, and the mechanisms by which genetic changes in these genes may affect growth plate chondrogenesis.

WG1-81 Bone and Growth Plate (BGP)

Role of obesity in the growth process and timing of puberty

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Background: Growth in children is influenced by the interaction of genetic and environmental factors. Nutritional status plays an important role in growth and body- weight regulation. The prevalence of obesity is increasing to epidemic proportions in children and adolescents.
Hypotheses: Excess adiposity during childhood affects growth and pubertal patterns.
Methods: Assessment of the evidence linking obesity and growth in animal models and observational studies in children.
Results: Studies report that children with exogenous obesity often have increased height velocity with tall stature for age despite low growth hormone levels. These findings are supported by the high levels of insulin and leptin observed in obese children, with a strong positive correlation between serum leptin concentration and percentage of body fat. Leptin secreted mainly from adipose tissue serves as a signal for the brain of the body's energy stores, and in animal models, it was shown to exert a direct effect on skeletal epiphyseal growth centers. Obese children (especially girls) were also found to mature earlier than lean children, suggesting that the degree of body fatness may trigger the neuroendocrine events that lead to onset of puberty. Accordingly, leptin receptors have been identified in the hypothalamus, gonadotrope cells, ovarian follicular cells, as well as Leydig cells, and leptin was shown to increase GnRH pulsatility in hypothalamic neurons and directly affect the anterior pituitary. The increased androgen levels documented in obese children may be implicated in their accelerated pubertal growth. Experimental studies have shown that leptin plays a specific role in stimulating the activity of enzymes essential for adrenal androgen synthesis.
Conclusions: Physicians should be aware that childhood obesity is associated with early puberty, premature adrenarche, and accelerated growth, with a possible impaired final height potential, all of which can affect quality of life.

WG1-82 Bone and Growth Plate (BGP)

Vitamin D in infancy - how much is needed

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Vitamin D is a prohormone synthesized in the skin or obtained from nutrition**.** One of the main functions of vitamin D is to maintain proper calcium and phosphorous homeostasis. In addition to its effects on tissues directly responsible for calcium homeostasis, vitamin D regulates the function of several other tissues. Consequently, vitamin D has been suggested a role in immune functions, cardiovascular diseases, diabetes, cancer and several other diseases. Vitamin D supplementation is widely used and several recommendations and guidelines have recently appeared, but the optimal serum 25(OH) D concentration is still under debate. The American Academy of Pediatrics (AAP) and the Institute of Medicine (IOM) defined the target S-25(OH)D as above 50 nmol/L (20 ng/ml), but many experts regard 80 nmol/L (32 ng/ml) as the desirable lower level. Breastfeeding is associated with vitamin D deficiency in the absence of supplementation. The IOM defined adequate vitamin D intake as 10 µg (400 IU) daily for infants up to age 12 months. Despite these recommendations, vitamin D deficiency is common, suggesting that the recommended dose is inadequate. In Finnish studies vitamin D deficiency was commong in newborns despite maternal vitamin D supplementation, and 20% of children at age 14 months had S-25(OH)D below 50 nmol/L despite vitamin D supplementation since age 2 weeks. Recent randomized controlled trials in infants have shown that vitamin D supplementation with up to 40 µg (1600 IU) daily from age 2 weeks to 3 months or 12 months is safe and causes no hypercalcemia or hypercalciuria. The 40 µg dose maintained S-25(OH)D above 80 nmol/L in all infants but resulted in S-25(OH)D levels above 125 nmol/L. More extensive and longer intervention studies are necessary to assess long-term effects and to define optimal vitamin D status for skeletal and non-skeletal functions in infants.

WG1-83 Bone and Growth Plate (BGP)

What is new in LRP5?

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It has been more than a decade since mutations affecting low-density lipoprotein receptor-related protein 5 (LRP5) were identified in patients who have abnormally low or high bone mass. Studies in flies and frogs initially suggested LRP5 functions as a Wnt co-receptor, and studies in humans and mice demonstrated the importance of Wnt signaling during skeletal patterning, growth, and homeostasis. These observations stimulated the search for drugs that, by altering Wnt signaling, could be used to treat common skeletal disorders like osteoporosis; at least 2 drugs are currently in clinical trials. I will summarize key findings and controversies regarding how LRP5 and Wnt signaling affect the skeletal system. I will also describe two proof-of-principle experiments in mice that address the feasibility of modulating Wnt signaling to improve bone properties in patients with Osteogenesis Imperfecta.

WG1-84 Bone and Growth Plate (BGP)

The effect of leukaemia therapy on linear growth and the development of bone strength

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Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer, with a cure rate that now exceeds 80%. As survival rates improve, the sequelae of ALL and its treatment are increasingly recognized, with skeletal health emerging as a clinically important care issue.
The skeletal morbidities that arise in this setting fall into three categories: osteoporosis (bone fragility), osteonecrosis (in situ bone death), and impaired linear growth. Osteoporosis and necrosis can be associated with excruciating bone pain, loss of mobility, fractures and skeletal deformity. Modest reductions in adult final height have been observed, including among patients without a history of cranial irradiation. This constellation of features highlights the deleterious impact of ALL and its treatment on focal and systemic bone metabolism.
Up to a third of children with ALL will develop fractures, symptomatic osteonecrosis or isolated bone pain in the first 5 years. Studies have shown that most of the bone morbidity occurs in the first two years. Vertebral fractures, an important but under-recognized manifestation of osteoporosis in children with leukemia, can be asymptomatic and thereby undetected. On the other hand, vertebral fractures at ALL diagnosis (including mild vertebral collapse) are the strongest predictor of incident fractures at 12 months. Older age and higher glucocorticoid doses (particularly with dexamethasone use) are among risks factors for osteonecrosis.
Different therapies have been attempted to treat or prevent bone morbidity in children with ALL, including calcium and vitamin D supplementation, calcitriol, and bisphosphonate therapy. Of these, bisphosphonate therapy is associated with the most potent bone-modifying effect, typically reserved for symptomatic osteoporosis and necrosis. In those with advanced osteonecrosis and limited potential for recovery, surgical intervention is warranted in select cases.

WG1-85 Bone and Growth Plate (BGP)

Phenotypes and genotypes: from TGF-ß to SHOX

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Abstract text has not been submitted.

WG2-86 Obesity (O)

Bone morphogenetic proteins (BMPs) in the regulation of thermogenesis in brown adipose tissue

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Background: Brown adipose tissue (BAT) can dispose of large amounts of glucose and lipid as heat. Increasing attention is being turned to the relevance of BAT to human physiology, thanks largely to studies reconfirming its presence and activity in humans. Strategies to increase sympathetic nervous system activation of BAT have been successful at reducing body weight but with detrimental cardiovascular effects. For this reason, mechanisms that enhance BAT activity independently of adrenergic receptors are of interest as potential targets for the treatment of metabolic disease. Bone morphogenetic protein 8b (BMP8B) is specifically expressed in BAT and mice lacking BMP8B are obesogenic.
Objective and hypotheses: We hypothesized that BMP8B was important for maintaining thermogenic capacity and aimed to dissect the mechanism through which BMP8B signaled to BAT and regulated energy balance in mice.
Methods: Genetically modified C57/Bl6J mice lacking BMP8B were challenged with standard and high fat diets and underwent comprehensive metabolic phenotyping. Brown adipocytes were analysed in terms of their response to norepinephrine following treatment with BMP8B. In addition the effects of central BMP8b treatment were examined due to our finding that BMP8B was expressed in the hypothalamus.
Results: Mice lacking BMP8B were found to have impaired thermogenic capacity and reduced metabolic rates, also lacking any metabolic response to a high fat diet. Treatment of brown adipocytes with BMP8B increased the response of key signalling kinases to norepinephrine. Central infusion of BMP8B was also found to specifically increase sympathetic nervous system activation of BAT.
Conclusions: BMP8B acts both peripherally in BAT and centrally in the hypothalamus to increase the thermogenic response to a given nutritional stimulus, acting to fine tune energy homeostasis through energy dissipation.

WG2-87 Obesity (O)

Mitochondrial dysfunction in white adipose tissue and obesity

Martin Wabitsch
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The capacity of lipid storage in white adipose tissue (WAT) and its capacity to expand determines the onset of metabolic disturbances associated with obesity (e.g. dyslipidemia, insulin resistance, glucose intolerance, hypertension). On the cellular level the capacity limits are characterized by the failure of vasculature to expand with adipocyte hypertrophy, cellular hypoxia and oxidative stress, impaired nutrient processing by the endoplasmatic reticulum as well as an impaired generation of new adipocytes from precursor cells. These cellular disturbances are associated with an altered adipokine secretion profile, macrophage infiltration into WAT, low-grade inflammation and fibrosis of WAT.
The mitochondrial energy metabolism plays a central role in these processes. Mitochondria provide key substrates and factors necessary for adipocyte differentiation, lipogenesis and lipid storage. Recent data support the idea that also in humans enhanced mitochondrial biogenesis as well as UCP-1 expression in white adipocytes may contribute to an improved oxidative capacity of WAT as well as to dissipitation of energy as heat by WAT.
In my presentation I will demonstrate the importance of mitochondrial function in adipocyte biology and metabolic health in obesity and how mitochondrial dysfunction leads to sick WAT and metabolic disturbances.

WG2-88 Obesity (O)

Regulation of obesity associated chronic inflammation and insulin resistance via apoptosis inhibitor of macrophage (AIM)

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Background: Obesity induces multiple metabolic and cardiovascular diseases, which is caused by chronic, low-grade inflammation initially observed in obese adipose tissues. In addition, etiological studies in humans have shown a strong correlation between obesity and autoimmune diseases. Furthermore, obesity is accompanied by fatty liver diseases including non-alcoholic steatohepatitis and hepatocellular carcinoma (HCC).
Objective and hypotheses: Our hypothesis is that there might be key molecules which are involved in the pathogenesis of all of these diseases, and thus regulate them. Based on recent studies, AIM appears to be one of the key molecules.
Methods: By employing obese AIM-deficient (AIM-KO) and control obese wild-type (WT) mice fed with high-fat diet (HFD), we extensively analyzed the pathology of these multiple diseases in these mice. Through this analysis, we investigated the molecular mechanisms of how AIM regulates these diseases.
Results: Under obese conditions, augmentation of blood AIM levels induces vigorous lipolysis in adipose tissue, thereby inducing chronic inflammation followed by diabetes and atherosclerosis In addition, in blood, AIM binds to IgM pentamers, and this association contributes to production of multiple autoantibodies under obese condition. Indeed, although AIM-KO mice showed advanced increase in body weight in response to HFD, chronic inflammation originated by macrophage infiltration into adipose tissue and following insulin resistance were reduced in these mice compared to WT mice. Consistently,

glucose intolerance and atherosclerosis induced in obese WT mice were dramatically tempered in AIM-KO mice. Contrastively, however, we also found that AIM strongly inhibits HCC development following fatty liver.
Conclusions: AIM may be a promising candidate of next generation therapeutic target for obesity-associated multiple diseases in modern society.

WG2-89 Obesity (O)

Declining β-cell function in children relative to insulin sensitivity with escalating OGTT 2-h glucose concentrations

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Abstract text has not been submitted.

WG3-90 Global Paediatric Endocrinology and Diabetes (GPED)

World issues in paediatric endocrinology

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The burden and threat of endocrine diseases in children constitutes a major challenge for development in the 21st century. Following a position statement of the original five pediatric endocrine societies on minimal acceptable care for children with pediatric endocrine disorders, representatives of all regional societies established Global Pediatric Endocrinology and Diabetes (GPED), as a non-profit, non-governmental organization that aims to improve the care of children with endocrine disorders who reside in resource-constrained environments, through advocacy, provision of training and educational opportunities, and development of research programs (Pediatrics 2013; 131 (2): e573-e578). Key to this approach is the recognition of specific deficits regarding prevalence of endocrine disorders, lack of trained personnel or diagnostic tools to address identified disorders, and limited resources for expensive medications and treatment tools and for research funding or collaborative studies that would provide implementation of public health interventions. It is currently endorsed by all regional societies for pediatric endocrinology and diabetes, and comprises 85 'Active Members' from developed and developing countries. http://www.globalpedendo.org/ Membership is open to all pediatric endocrinologists. Some of GPED's current projects include 1. A primary aim of the GPED task force is to create and establish educational opportunities for pediatric health care workers in field identification of pediatric endocrine emergencies and the use of growth charts. 2. Develop a GPED consensus on the WHO Charts. 3. Develop CAH support groups in developing countries. Members of the pediatric endocrine community are welcome to join GPED.

WG3-91 Global Paediatric Endocrinology and Diabetes (GPED)

Global paediatric endocrinology and diabetes (GPED): a joint effort by world paediatric endocrinologists

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Non-communicable diseases (NCDs) are a major cause of global mortality. In many low-income settings, medical care for endocrine conditions and for diabetes is absent or suboptimal. Global Pediatric Endocrinology and Diabetes (GPED, www.globalpedendo.org) was founded in 2010. Its mission is to improve the care of children living in developing countries and presenting with endocrine disorders or with diabetes. GPED aims at working with health professionals, corporations, governments and non-profit organizations across the world. In a recent position paper (Zacharin et al, Pediatrics 2013; 131: e573), GPED members have identified six major areas of need that are consistent with GPED's mission: 1. Determination of the prevalence of specific pediatric endocrine disorders in developing countries; 2. Training and education of health professionals to ensure recognition of pediatric endocrine disorders;3. Linking with expert opinion leaders throughout the world around clinical care issues; 4. Availability of diagnosis and management tools that are tailored to the needs and capacity of the community; 5. Collaboration between pediatric endocrinologists and government authorities for the implementation of simple public health measures; and 6. Promotion of quality research projects that address the clinical needs of low income countries.
The executive committee of GPED consists of the Officers and of a member from each of the following regional societies: Asian-Pacific Pediatric Endocrine Society (APPES), African Society for Paediatric and Adolescent Endocrinology (ASPAE), Chinese Society for Pediatric Endocrinology and Metabolism (CSPEM), European Society for Paediatric Endocrinology (ESPE), International Society of Pediatric and Adolescent Diabetes (ISPAD), Indian Society for Pediatric and Adolescent Endocrinology (ISPAE), Japanese Society of Pediatric Endocrinology (JSPE), Pediatric Endocrine Society (PES) and Latin American Society for Pediatric Endocrinology (SLEP).

WG3-92 Global Paediatric Endocrinology and Diabetes (GPED)

Paediatric endocrinology management in low resource societies

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Normal trajectories of growth and puberty fundamentally reflect physical, emotional and psychosocial health of children. Achievement of optimal growth, normal pubertal completion, with potential for fertility must be primary aims for paediatricians. The Paediatric Endocrinologist has a major role to play in ensuring realization of these ideals.
In countries with high standards of living, rapid access to accurate health management is expected. By contrast, in societies with limited resources, many factors limit access to care, including transport, poor recognition of illness, lack of awareness to source assistance, compounded by fear, distrust and secrecy, when education may be incomplete. Paediatricians are over-burdened with enormous workloads and minimal primary resources. First identification of a child's health is often made by a health visitor, whose training may be suboptimal. Access to specialized knowledge, technical expertise and even basic technologies is frequently limited.
Areas of need include

1. Better identification of chronic illness and growth
2. Improved availability and choice of basic tools for assessment
3. Expertise to choose appropriate tests, balancing value versus cost of medication
4. Expertise in family education to encompass knowledge, social mores, cultural and tribal differences, complex problems of fear and secrecy including possible exclusion or expulsion from society due to health problems.
5. Establishment of mechanisms and need for follow-up
6. Prioritisation of action based on accurate information.

Areas to be addressed include education and support for staff and families, provision of tools, educational resources and training laboratory staff.
Identification of need may be country-wide, addressing large scale health problems as well as specific disorders. Education and research need to be matched with responsibilities of the medical community, pharmaceutical and government resources, to promote and support these programs.

WG3-93 Global Paediatric Endocrinology and Diabetes (GPED)

The changing face of diabetes in Africa

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Background: Diabetes has assumed an increasing prevalence and prominence globally. Irrespective of this fact the actual burden of diabetes in the sub-Saharan African region is not really known.
Objective: To share the insight into the challenges and progress of childhood diabetes in Africa
Methodology: Literature review, oral presentations, unpublished research, updated country register
Results: There is dearth of information as concern childhood diabetes in Africa. Programs like Life for A Child (LFAC), Changing Diabetes in Childhood (CDiC) in various African countries have made tremendous im-

pact on the care and awareness in the countries were they are present. Just as important an impact through ESPE, ISPAD and WDF is the creation of Pediatric Endocrinology Training Center in Africa, Nairobi, Kenya (PETCA) and Pediatric Endocrinology Training Center in West Africa, Lagos, Nigeria (PETCWA) which have produced Pediatric Endocrinologist that have spread throughout Africa in the past seven years.
The graduates from these centers have improved the level of previously practiced standard of care. Despite these developments, the progress achieved thus far was not enough to cause a revolution in the story of diabetes on the Continent.
There are myriad of challenges such as a lack of knowledge as to the exact prevalence and incidence of childhood diabetes. Also no access to insulin by a wide area of the continent (not readily available or affordable). Many countries are still without the appropriate personnel to ensure a minimal standard of care.
Conclusion: The dearth of awareness amongst the general populace and the medical personnel, lack of prevalence or incidence indices and research has made it difficult, to know the exact burden of diabetes in childhood on the continent. Obviously, the continent has a lot to learn and understand the characteristic of childhood diabetes amongst African children.

WG3-94 Global Paediatric Endocrinology and Diabetes (GPED)

At last, an adult height prediction model for black children

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Background and objective: 61 years after Bayley and Pinneau presented their model for adult height prediction (AHP) in Caucasian children, we present the first model valid for black children.
Methods: This work is based on the longitudinal "Birth to twenty" study of black and white children born in 1990 in South Africa. We included 448 children, 74% black and 26% white, with 4-9 X-rays of the left hand each, recorded at ages 9-17 y. At the last visit, they were on average 0.8 cm from adult height, and the black participants had on average 7 cm lower adult height than the white.
Results: The BoneXpert Caucasian AHP model was found to predict the adult height well for the white children, with no significant bias and a root mean square (rms) error of prediction of 3.2 cm for boys and 2.7 cm for girls (all results refer to boys with BA 9-14 y, and girls with BA 9-13 y). In the black children, this AHP model overestimated the adult height by on average 1.4 cm for boys and 2.2 cm for girls. We propose an AHP model for black children consisting of the Caucasian AHP model with a simple correction of this bias, and this model has rms error 3.3 cm for boys and 3.0 cm for girls.
We also derived reference curves for bone age advancement, i.e. the average bone age minus age, versus age, and compared them to curves of normal North-American children from 1997. At age 10, we found white South Africans to be 0.2 years behind white Americans, while black South Africans were 1.0 years behind black Americans.
Conclusions: We conclude that black South African children matured later than black American children. The Caucasian AHP model overestimated their adult height by 1%, and we proposed a modified model for black children, which predicted with no bias and with satisfactory accuracy.

WG3-95 Global Paediatric Endocrinology and Diabetes (GPED)

Reduction in incidence of type 1 diabetes mellitus complications in adolescents in Uzbekistan

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Background: The work was initiated to perform comparative assessment of type I diabetes mellitus (DM) compensation degree and prevalence of complications in adolescents within the period from 1998 to 2012 as per screening data.
Methods: In 2012 in the WDF frames a cross-sectional screening of 538 adolescents with type I DM (with 100% coverage) was conducted in Uzbekistan aiming at assessment of diabetes compensation degree and incidence of its chronic complications as compared with the screening of 450 adolescents performed in 1998 (with 93% coverage).
Results: In 2012 achievement of target therapy goals (< 7.5%) was 13.3% as compared with 1998 (11.8%), mean HbA1c reducing from 11.4% to 10.0%. Comparative analysis demonstrated confident reduction in incidence of physical development delay from 44.2% to 17.3% (P< 0.0001) and sexual development retardation from 49.1% to 14.3%, that is, almost by three times (P< 0.0001). Number of adolescents with diabetic retinopathy reduced from 39.3% to 12.5% (P< 0.0001), those with diabetic polyneuropathy - from 56.0% to 47.0%. There was 4-fold reduction in the number of adolescents with IV-V degree diabetic nephropathy (from 51.0% to 10.8%; P< 0.0001), diabetic chairopathybeing decreased from 40.3% to 27.2% (P< 0.001). Number of adolescents with cataract reduced, though unconfidently, from 7.1% to 5.4%.
Conclusions: Thus, the findings from the screening demonstrated efficacy of the National Register and adequate choice of strategy and tactics for optimization of preventive and medical aid for adolescents with type I DM in Uzbekistan.

WG3-96 Global Paediatric Endocrinology and Diabetes (GPED)

Congenital hypothyroidism: world birth population undergoing newborn screening and economic impact

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Background: Congenital hypothyroidism (CH), with a reported incidence ranging from 1:2,000 to 1:4,000 newborns, is one of the most common preventable causes of mental retardation. Detection by newborn screening (NBS) and early treatment of infants can largely eliminate the intellectual disability caused by this disorder. Screening of newborns has been in existence for over 50 years, and screening for CH was adopted by developed countries starting in the mid-1970s.
Objective and hypotheses: Newborn screening for CH is now expanding to less developed countries. However, it is unknown what proportion of the world birth population undergoes screening for CH. The first objective of our study was to determine the percentage of the world birth population undergoing screening for CH. The second objective was to determine the economic burden of undetected cases of CH worldwide.
Methods: We undertook a search using PubMed and Google for all existing newborn screening programs worldwide in countries with a population greater than one million.
Results: Based on our search for current screening programs, approximately 71.4% percent of babies worldwide are not born in an area with an established NBS program. At a lifetime cost of more than one million dollars (USD), the annual cost of CH cases not identified and treated early by NBS programs is conservatively estimated at approximately 30 billion dollars (USD).
Conclusions: Based on our data, it is estimated that 30,000 babies with CH worldwide are born each year outside a NBS program. Thus, despite the existence of screening for over five decades in developed countries, the majority of babies with CH worldwide are not detected and treated early. The economic burden of retardation owing to CH remains a significant public health challenge.

WG3-97 Global Paediatric Endocrinology and Diabetes (GPED)

Newborn screening for congenital hypothyroidism in an underprivileged region of India

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Background: In India newborn screening (NBS) is still in its nascent stages due to economic constraints and lack of awareness.
Objective and hypotheses: To evaluate feasibility and recall rates in a NBS program for CH in an underprivileged population in India.
Methods: Post natal heel prick samples were collected on Whatman 903 filter papers at 24 to 96 hours of life for TSH assay by immunofluorescence. Babies with screen TSH 20 - 40 miu/L serum units were recalled for repeat filter paper TSH at 10 days. Those with screen TSH > 40miu/L were immediately recalled for serum TSH and T4. After the first 6000 babies, in view of high recall rates, age related cut offs were used: TSH>34miu/l during 24-48 hours of life and >20miu/L after 48 hours.
Results: 13,760 newborns from 7 urban and rural hospitals were screened. Majority (65%) of the families belonged to the lower and 34 % to middle socioeconomic strata. Five percent mothers refused screening and 85.7 % of those recalled came for confirmatory sample. Using 20miu/l cutoff, recall rate was 1.41 %. With age related cutoffs, recall was lowered to 0.87 %, though still high. Mean+sd TSH was 7.1±9.3 miu/L at 24-48 hours, 6.5 ±4.4 at 48 to72 hours and, 5.7 ± 4.4 at > 72 hours. Eleven babies had CH. Eight have permanent CH (1 athyreosis, 2 Lingual, 1 NIS defect, 4 other dyshormonogenesis). One has refused therapy.
Conclusions: With adequate counseling NBS can be implemented even in underprivileged regions of India with fair success. Age related cutoffs may be necessary to deal with the high recall rate resulting from early discharge and neonatal TSH surge. Iodine deficiency as a cause of high recall rate needs to be investigated.

WG3-98 Global Paediatric Endocrinology and Diabetes (GPED)

Dyshormonogenesis seems to be more frequent in a group of Cameroonian patients with congenital hypothyroidism

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Background: Congenital hypothyroidism is the first preventable cause of mental retardation, occurring in 1/3000 births worldwide. But with ethnic variability exist; so it seems to be rarer in African population (1/10000 to 1/320000). Neonatal screening is the best way of early diagnosis but in Subsaharan African, in its absence, the diagnosis is clinical with many misdiagnoses. In this context, little is known about clinical presentation and etiology of congenital hypothyroidism.
Objective and hypotheses: To describe clinical presentation and etiology of congenital hypothyroidism in Yaounde. Cameroon.
Methods: Medical records of all children (4 girls, 4 boys) with congenital hypothyroidism diagnosed during the last 3 years in a single centre of pediatric endocrinology in Cameroon were retrospectively reviewed.
Results: Children were brought for mental retardation (n=3), growth retardation (n=2), macroglossia with hypotonia (n=2), abnormal skin (n=1). Median age at diagnosis was 1.7 years (range 0.25-13.9 years). There was no consanguinity but close ethnic origin. Main general clinical signs were sleepiness (n=4), constipation (n=4) ombilical hernia (n=2). On the 5 children less than 3 years, 2 had a large anterior fontanel. The Denver score used for psychomotor development was abnormal for 7/8 patients, particularly on sociability (n=5) then language (n=2) and fine motricity (n=2). The median initial TSH level was 134.15 mUI/L(range 6.7-643). On cervical ultrasound, a goiter was present in 3, normal thyroid gland in 2, hypoplastic gland in 2, absent in one. The latter had had a surgery for a "sub maxillary cervical nodule". Scintigraphy was not available for the patients, but all patients' present improvement under treatment.
Conclusions: Thyroid dyshormonogenesis seems to be more frequent in our center, in the context of hypothyroidism. The diagnosis is still late in the absence of neonatal screening.

WG4-99 Paediatric and Adolescent Gynaecology (PAG): Hyperinsulinaemic Androgen Excess (PCOS) in Adolescents

Early development and prevention of PCOS

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PCOS is traditionally viewed as an ovarian disorder that emerges in adolescence and may lead to metabolic complications in adulthood. Recent insights, however, suggest that PCOS is a disorder of adipose-tissue hyperexpansion that may originate in early life, develop across childhood and puberty, and advance into end-stage disease (with ovulatory dysfunction & androgen excess) by adolescence.
In this concept, major risk factors for PCOS are adipose-tissue hypoplasia in early life (leading to a lower number of adipocytes in later life, for example, in girls born small) and an obesogenic lifestyle in childhood (leading to an absolute or a relative excess of lipogenesis). Prepubertal ensembles pointing to PCOS risk include visceral adiposity, high levels of circulating triglycerides, insulin, IGF-I & DHEAS, and low levels of adiponectin and SHBG.
The new concept on the ontogeny of PCOS does not only harbour the most common (obese and non-obese) phenotypes of PCOS, but implies also a potential to prevent PCOS by preventing the hyper-expansion of adipose tissue in childhood and puberty. This preventive potential was first tested in non-obese girls known to be at high risk for PCOS, namely low-birthweight girls with precocious pubarche. Early metformin treatment for 4 yr (age 8-12 yr) was associated with post-pubertal reductions in visceral and hepatic adiposity and in the prevalence of PCOS (5% vs 52% after 8 yr of study, thus 4 yr after stopping metformin). Welcome epiphenomena of such early metformin intervention were an increment of adult stature (by about 4 cm towards normal) and a delay of menarche (by about 1 yr towards normal).
Worldwide, the early prevention of PCOS should become a focus of pediatric attention.

WG4-100 Paediatric and Adolescent Gynaecology (PAG): Hyperinsulinaemic Androgen Excess (PCOS) in Adolescents

Genetics of PCOS

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Polycystic ovary syndrome (PCOS) displays familial clustering, indicative of a multigenic aetiology. While several hypotheses have been proposed for candidate genes involved in gonadotropin secretion, steroid hormone synthesis, insulin signalling and chronic inflammation, none have been robustly substantiated until very recently. Genome-wide association studies (GWAS), which genotype hundreds of thousands of common genetic variants located across the genome, have successfully identified many specific genetic determinants in other complex diseases; the findings often highlight previously unsuspected mechanisms. Very large sample numbers are required to provide sufficient power to meet the stringent GWAS statistical thresholds designed to avoid false-positive findings.
Recently, a large GWAS for PCOS was published (Shi et al. Nature Genetics Sept 2012;44:1020-5) based on GWAS data from 2,254 PCOS cases and 3,911 control women from reproductive and gynaecology clinics throughout China. Replication involved a further 8,226 cases and 7,578 controls. In total, eleven genetic loci were robustly associated with PCOS. Genes related to insulin signalling, sex hormone function, type 1 and type 2 diabetes substantiated earlier hypotheses regarding the aetiology of PCOS. Association signals in other genes related to calcium signalling and endocytosis provide new directions for future studies to understand the biological mechanisms in PCOS. Notably, of the 1,618 separate GWAS publications listed on www.genome.gov, a central catalogue of GWAS findings, there are only three studies for PCOS, two in Chinese and one in Korean women. In the recent Chinese study, mean BMI in PCOS cases, 23-24 kg/m^2, was far lower than average BMI in European and North American PCOS studies, 30-37 kg/m^2, and this likely en-

hanced their power to identify genetic factors for PCOS. Further approaches to narrow the broad heterogeneity in PCOS outcomes within individual studies may also be fruitful.

WG4-101 Paediatric and Adolescent Gynaecology (PAG): Hyperinsulinaemic Androgen Excess (PCOS) in Adolescents

Hyperinsulinaemic androgen excess in patients with type 1 diabetes

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Modern therapy of type 1 requires multiple daily insulin doses that are administered with the aim of achieving optimal metabolic control. This type of treatment is associated with higher serum insulin that may lead to overstimulation of the insulin and IGF-1 receptors in the ovary, increasing androgen secretion and fostering the development of PCOS. When the pancreas secretes insulin into the portal circulation under physiological conditions, the liver is the organ exposed to the highest insulin concentrations, and it eliminates an important fraction of the secreted insulin. In T1D patients, insulin administered to the subcutaneous tissue is absorbed into the systemic circulation, omitting this hepatic first-pass step and exposing the peripheral tissues to supraphysiological insulin levels.
Hyperandrogenism has been classically associated with insulin resistance and type 2 diabetes, but increasing evidence shows that T1D women may also exhibit this abnormality. Girls with T1DM exhibit increasing androgens and signs of incipient functional ovarian hyperandrogenism at the end of puberty. In adult women a prevalence of 40% of clinical or biochemical hyperandrogenism has been shown, but this problem has a milder magnitude compared to non-diabetic PCOS women.
An association of hyperandrogenism with intensive insulin treatment, but not total daily insulin dose, and with premenarcheal onset of DM has been described. This talk will review clinical data, physiopathology and treatment of abnormalities of androgen levels in patients with T1DM (FONDECYT GRANT 1050452 and 1100123).

WG4-102 Paediatric and Adolescent Gynaecology (PAG): Hyperinsulinaemic Androgen Excess (PCOS) in Adolescents

PCOS in girls: what the world can learn from India

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Polycystic ovary syndrome remains one of the commonest endocrine disorder in women in the reproductive age group, with an estimated prevalence of 6-10%. A form of insulin resistance intrinsic to this syndrome is believed to play a central role in its pathogenesis. Insulin resistance and associated hyperinsulinia links PCOS to its metabolic abnormalities At the same body mass index, Indians have more insulin resistance as compared to Caucasians. So is prevalence of PCOS higher in Indians and are the metabolic characteristics similar to girls with PCOS of Caucasian origin.
Prevalence of PCOS was studied in girls from 3 different colleges (n=2150), 1520 (70.7%) agreed to participate. Of the 1520 girls, 200 (13.1%) were labeled as probable cases; 27 girls were confirmed to have PCOS. a calculated prevalence of 3.7% (95% CI, 2.6-4.4) in this population. The mean age of these PCOS cases was 18.96 ± 1.73 yrs, body mass index was 21.72 ± 5.48 Kg/m^2 and waist hip ratio 0.81 ± 0.08. Only 12% girls had a body mass index ≥ 27.5 Kg/m^2, but 44% had waist hip ratio > 0.81, again highlighting that despite low BMI, Indians have more abdominal obesity.
Seventy nine girls were prospectively followed for 1 year in our clinic. Ten percent had hypertension and 30% girls had hyperlidemia, 14% girls had metabolic syndrome, 16 had abnormal glucose tolerance in the form of impaired glucose tolerance (12) and impaired fasting glucose (4). None had diabetes. Comparing the girls with abnormal glucose tolerance with normal glucose tolerance, there was no statistical difference in their mean age, BMI of waist circumference. Prevalence or hypertension, metabolic syndrome or family history of diabetes also did not differ in the two groups. Prevalence of abnormal glucose tolerance was similar in both lean and overweight or obese girls with PCOS (OR 0.77, P=0.68).
Indian girls with PCOS are lean but have abdominal obesity. Prevalence of metabolic abnormalities is similar.

WG4-103 Paediatric and Adolescent Gynaecology (PAG): Hyperinsulinaemic Androgen Excess (PCOS) in Adolescents

Treatment of PCOS in obese girls: weight loss, oral contraceptives and/or insulin sensitisation

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Abstract text has not been submitted.

WG4-104 Paediatric and Adolescent Gynaecology (PAG): Hyperinsulinaemic Androgen Excess (PCOS) in Adolescents

Treatment of PCOS in non-obese adolescents

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PCOS is a common endocrinopathy in women that has traditionally been viewed as an ovarian disorder. Accordingly, the classic therapeutic approach, also for adolescents without pregnancy risk, is to silence the ovaries with an oral contraceptive (OC). Recent evidence suggests that PCOS is primarily a disorder of hyperexpansion of subcutaneous adipose tissue, implying that intervention should rather aim at reducing this abnormality thereby also correcting the associated insulin resistance, visceral adiposity and low-grade inflammation.
For nearly a decade it has been known that a low-dose combination of flutamide (Flu, an androgen-receptor blocker) and metformin (Met, an insulin sensitizer) is superior to a drospirenone-OC in correcting the endocrine-metabolic and body-composition anomalies of non-obese adolescents who are not at risk of pregnancy.
Recently, the effects of low-dose Pioglitazone-Flutamide-Metformin (PioFluMet) were compared to those of an OC with ethinylestradiol-cyproteroneacetate (EE-CA). Both treatments attenuated the markers of androgen excess similarly, but they had diverging effects on visceral and hepatic adiposity, on low-grade inflammation (as judged by CRP) and on cIMT; 6 months post treatment, menstrual regularity and insulinemia (during an oGTT) were still different. All these differences were to the advantage of low-dose PioFluMet.
In conclusion, the strategy whereby androgen excess is reduced in adolescence does not only influence the overall phenotype during the intervention but also thereafter (for at least 6 months but potentially into adulthood). Low-dose PioFluMet tends to normalize the endocrine-metabolic state of non-obese adolescents with PCOS and - in contrast to an OC - may prevent part of the androgen-excess phenotype in adulthood, including adiposity and subfertility.

WG4-105 Paediatric and Adolescent Gynaecology (PAG): Hyperinsulinaemic Androgen Excess (PCOS) in Adolescents

Contraceptive options for adolescents with PCOS

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Adolescents with polycystic ovary syndrome (PCOS) may present to their pediatrician, endocrinologist, or gynecologist for contraceptive counseling, in addition to management of their hyperandrogenism. These patients present unique issues to the health care team, including the effects of hormonal contraception on hirsutism and menstrual regulation, in addition to potential

alteration of glucose homeostasis, skeletal turnover, and thrombotic risk. This presentation will provide an overview of contraceptive methods that are currently available to adolescents, with a focus on combined oral contraceptive pills (OCPs), the transdermal patch, and vaginal ring.
The presentation will then focus on thrombotic risk and bone health as outcomes that may be affected by these contraceptive methods. Issues that arise in the care of young women with PCOS will be highlighted, as they may exhibit hirsutism, acne, hyperinsulinism, and/or glucose intolerance. Each method and the evidence presented will be evaluated in light of recent WHO and CDC contraceptive recommendations.
Lastly, the role of insulin sensitizers in the care of these young women with be considered, as monotherapy and in combination with an OCP.

WG5-106 Turner Syndrome (TS): Controversies on the Care of TS

Ovarian failure in TS

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Abstract text has not been submitted.

WG5-107 Turner Syndrome (TS): Controversies on the Care of TS

Puberty induction in TS: early, late or super early

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Estrogen replacement therapy in adolescence: The goal of estrogen therapy in Turner syndrome is to correct the estrogen deficiency in a manner that optimizes final height, permits attainment of normal bone mass, and provides appropriate feminization with minimal risk of adverse affects. Estrogen replacement in adolescence is also important for mood and self-image. Recent research indicates that estrogen used in childhood may also have positive effects on cognition and growth.
The issues to be resolved include the age at which estrogen replacement should commence, the route of administration, the dose and regimen of dose increase during adolescence, the timing and nature of progesterone administration, and the total duration of treatment.
The available data suggests that treatment should be initiated between 10 and 12 years of age. Whether treatment should start even earlier, at very low doses, is the subject on ongoing research. We will review results of a recent study comparing the metabolic effects of route and type of estrogen replacement (oral versus transdermal [TD] $17\beta E_2$), using estrogen concentration-based dosing in adolescent girls with TS. Overall, both oral and transdermal $17\beta E_2$ are suitable choices to feminize girls with hypogonadism, but TD administration appears more physiologic. The importance of estrogen in maintaining normal bone mass suggests that treatment should be long-term.

WG5-108 Turner Syndrome (TS): Controversies on the Care of TS

TS patient as a candidate for IVF

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Background: Infertility is one of the typical features in Turner syndrome, but as we have shown, many of these girls have still ovarian follicles and oocytes in their ovaries as teenagers. Up to 30 % are fertile up to young adulthood, but almosta all undergo early ovarian failure.
Objective and hypotheses: Ovarian tissue and/or oocytes can often be cryostored from adolescent Turner girls. Some of them can obtain spontaneous pregnancies at young age.
Methods: From prepubertal girls with signs of spontaneous puberty and having mosaic Turner syndrome, it is worthwhile to cryostore some 25% of cortical tissue from one ovary. If ovarian follicles are seen in an ultrasound scan, ovarian stimulation for in vitro fertilisation (IVF) and vitrification of the eggs can be performed. leter on, when it is time for aprgenancym the tissue can be transplated back to the ovary, or the eggs fertilised and transferred to the Turner womans pregnancy, but never nore than one embryo at a time to avoid the risks caused by a multiple pregnancy.
Results: The risk of aortic dilatation and rupture among these girls is high. Hence, aortic MRI har to be performed before and during an attempted pregnancy. If the risk of rupture is considered high, abstaining from pregnancy can be counselled.
Conclusions: Many young women, particularly those with spontaneous signs of pubertly adn mosaic Turner can benefit from assisted reproduction and IVF in careful follow-up.

WG5-109 Turner Syndrome (TS): Controversies on the Care of TS

Cardiac evaluation in TS using new imaging techniques: is MRI the first-line study also in paediatric population with TS?

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Congenital defects including most commonly aortic valve disease and aortic arch and pulmonary vein anomalies affect approximately 40% of girls and women with TS. These defects are often clinically silent in young patients, presenting later in life with irreversible damage to the valve, aortic catastrophe or right heart failure.
Complications of congenital heart disease (CHD) contribute to increased morbidity and mortality in TS. In 2007, a consensus group recommended that all newly diagnosed patients with TS should have specialist clinical evaluation with transthoracic echocardiography (TTE), regardless of age. Additional screening with cardiac MRI was recommended for girls old enough to cooperate without sedation, and for all newly diagnosed adults. While TTE allows visualization of aortic valve and ascending aorta in infants, it is much less helpful in older patients. This is because ultrasound waves are impeded by bone, air and adipose tissue and decay with distance from the transducer. Measurement of aortic blood flow with Doppler ultrasound was previously thought sufficient to detect aortic valve abnormality or coarctation, but the risk for aortic dilation/dissection may be independent of flow abnormality, so we accurate views of the cardiovascular anatomy and measurements of aortic diameter are essential to guide the management of older girls and adults with TS. For this reason we recommended cardiac MRI at an age when the girl is able to cooperate with the study without the need for sedation. A cardiac MRI evaluation generally requires the patient to lie still for 10-20 minutes with a heart rate less than 90 bpm, so most girls will be at least 7-8 years old for the screening study.
This advice pertains to the use of cardiac MRI for screening purposes only; if there is a clinical indication, then cardiac MRI with sedation as necessary is certainly appropriate.

WG5-110 Turner Syndrome (TS): Controversies on the Care of TS

Transition of females with TS from paediatrics to adulthood: the paediatric endocrinologist

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Background: A key period in the lifespan of an adolescent with the Turner syndrome is the transition from pediatric-centered care to that of adult-oriented care.
Objective and hypotheses: Transition means to pass from one place to another. It is a process, not a single event. The goals are to make this process seamless, patient and family oriented and outcome driven. It leads to an event: the transfer.
Methods: To be successful one must start early and foster personal health-related responsibility. The general principles are that the process be planned, gradual, collaborative, address issues common to all adolescents and chronologically and developmentally appropriate. One may have to overcome some barriers at the individual, family/parent, provider and health system levels. For adolescents with the Turner syndrome it must address issues related to the endocrinological, cardio-vascular, gynecological (and fertility), psychological, and sensory systems, for the linear growth and entry into and progression t6hrough puberty should have been completed. The major areas of concern are related to fertility, hypertension, non-alcoholic fatty liver disease (NAFLD), bone and hearing.

Conclusions: Transition to adult care from family-center pediatric care is a process and not a single event. One must start early and focus on this process for several years before the transfer is made. For adolescents with the Turner syndrome there will likely be several adult-oriented physicians involved--usually at least a general endocrinologist and a gynecologist.

WG5-111 Turner Syndrome (TS): Controversies on the Care of TS

Transition of females with TS from paediatrics to adulthood: the adult endocrinologist

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Treatment with growth hormone (GH) during childhood and adolescence allows a considerable gain in adult height. SHOX deficiency explains some of the phenotypic characteristics in TS, principally short stature. Puberty has to be induced in most cases, and female sex hormone replacement therapy (HRT) should continue during adult years. These issues are normally dealt with by the paediatrician, but once a TS female enters adulthood it is less clear who should be the primary care giver. Morbidity and mortality is increased, especially due to the risk of dissection of the aorta and other cardiovascular diseases.
The proper dose of HRT has not been established, and, likewise, benefits and/or drawbacks from HRT have not been thoroughly evaluated. In most countries it seems that the transition period from paediatric to adult care is especially vulnerable and the proper framework for transition has not been established. Today, most treatment recommendations are based on expert opinion and are unfortunately not evidence based, although more areas, such as GH treatment for increasing height, are well founded.
During the transition period many young females opt out of longitudinal follow-up, probably because they feel well and cannot clearly see the need for continued medical surveillance. However, osteoporosis, diabetes, both type 1 and 2, hypothyroidism, obesity and a host of other endocrinological diseases and conditions are seen more frequently in Turner syndrome in the long term. Prevention, intervention and proper treatment is only just being recognized. Hypertension is frequent and can be a forerunner of cardiovascular disease.
The description of adult life with Turner syndrome has been broadened and medical, social and psychological aspects are being added at a compelling pace.
In summary, Turner syndrome is a condition associated with a number of diseases and conditions which need the attention of a multi-disciplinary team during adulthood.

WG6-112 Disorders of Sex Development (DSD): Information and Communication in the Context of DSD

DSD: biochemical information necessary to reach a diagnosis

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Disorders of sex development (DSD) comprise a broad range of biological variants which have been grouped into pathophysiologic entities by a new nomenclature reached at the Chicago consensus meeting 2005. But, diagnosing DSD remains a difficult task that still remains elusive in (too) many cases, even when using a multi-disciplinary approach. Clinical, biochemical, genetic as well as imaging studies may be employed to reach a final diagnosis. Among them, biochemical studies play an important role as first and second line investigations. In the newborn period, basal testing in an infant with ambiguous genitalia may include serum measurements of electrolytes, glucose, 17-hydroxyprogesterone, cortisol, testosterone, androstenedione, gonadotrophins, anti-Müllerian hormone (AMH; MIS) as well as urinary steroid profiling. These investigations together with the clinical evaluation (history and physical exam), an ultrasound and karyotype allow a first definition of the DSD problem and provide essential information concerning sex of rearing, possible (adrenal) co-morbidities and final diagnosis. Depending on the results further biochemical investigations are undertaken such as hCG, LHRH and ACTH stimulation tests to assess gonadal and adrenal steroidogenesis and function. It is crucial for biochemical test interpretation that (pre-) analytical procedures are accurate and that age- and sex-specific normative values as well as limitations of specific assays are known. Especially immunoassays for steroid measurements are often too unspecific to reveal informative results and are about to be replaced by more specific mass spectrometric methods (LC-MSMS, GC-MS) that also bear the advantage of providing not only a single steroid but a full profile. Indeed, it is the characteristic metabolic profile which often leads to the specific diagnosis which is then confirmed by genetic methods.

WG6-113 Disorders of Sex Development (DSD): Information and Communication in the Context of DSD

Chances, pitfalls, risks and how genetic information should be relayed to the clinician

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New sequencing technologies are dramatically changing biomedical research and patient diagnosis. The reducing sequencing costs mean that the technology is increasingly available. It has already revealed an unanticipated degree of genetic variation with many predicted deleterious mutations present in the general population that can hinder the phenotypic interpretation. This makes the identification of disease-causing mutations in individuals with DSD a challenge. Therefore, in the short term, a goal in the field of DSD should be the discovery of a core group of genes that are recurrently mutated and unequivocally cause the disease. The current focus on sequencing exomes, rather than the entire genome should uncover a great number of relevant targets in a cost-efficient and easily interpretable manner. The availability of genomic sequences of a DSD patient will lead to an emphasis the need for a highly accurate clinical description of the phenotype using standardized precise protocols. Assuming that a genetic diagnosis of DSD can be achieved, one major outstanding issue is how to deal with incidental genetic findings. Each exome will reveal mutations in genes, unrelated to the purpose of the diagnostic sequencing and whose potential effect on health is unknown. Should there be disclosure of such incidental findings? Currently there is no single database available that represents an accurate compendium of known pathogenic variants, nor is there an automated algorithm to identify all novel variants meeting criteria for pathogenicity. Does the clinician have a responsibility to check through all of the variants and identify known pathogenic mutations that could predispose the patients to other diseases? Should the patient have the right of access to such information? There is an urgent need for guidelines to be established before the use of exome sequencing emerges as a routine clinical diagnostic application.

WG6-114 Disorders of Sex Development (DSD): Information and Communication in the Context of DSD

Communication around the DSD patient in the clinical setting

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Optimal communication is the cornerstone of good clinical practice. This is especially the case when managing complex conditions within the setting of a multidisciplinary team. The paediatric endocrinologist is often situated at the centre of the DSD team and acts as a conduit for communication. Detailed guidance around communication with parents and members of the MDT were issued in the UK DSD guidance document in 2011. This review will illustrate models of communication that may exist within the DSD team and explore novel methods that could facilitate future developments.

WG6-115 Disorders of Sex Development (DSD): Information and Communication in the Context of DSD

Decision impossible - What does the parent want/need to hear?

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Private Speaker, Potsdam, Germany

Despite concerns from people living with intersex conditions as well as outcries from human rights groups, so called "genital constructive surgery" is still general practice for newborn and underage patients diagnosed with DSD. Not only acting at the risk of assigning a sex at a very early age that turns out to be incongruent with the patient's actual gender identity, but also risking sexual insensitivity and life-long pharmaceutical hormone replacement - not to speak of possible cases of inflicting infertility - all without patient consent, doctors want to help parents at a loss of how to raise a child with ambiguous genitalia. The presenter will make a case for the need to help parents with this pressing concern not by performing surgery on the child but by offering psychological and other social support in a situation that may turn out less challenging than it first appeared. The presenter is mother of a child born with an intersex condition.

WG6-116 Disorders of Sex Development (DSD): Information and Communication in the Context of DSD

Communication with children and adolescents about their DSD condition

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The question is not: To tell or not to tell children or adolescents about their DSD condition. The question is when and how to tell. Presented is one model of how to inform children and adolescents about their DSD diagnosis or condition. This model, which can be used by parents, provides a template upon which various DSD diagnoses can be placed to educate children and teenagers about their condition. The model can be adapted to be used over time or in the case of selected adolescents used in one session. The importance of follow up and iterative learning will be stressed. The goal of such communication is to replace anxiety and unease with a degree of comfort and acceptance about how they were born.

WG6-117 Disorders of Sex Development (DSD): Information and Communication in the Context of DSD

The I-DSD registry update

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Background: Effective clinical care and research in Disorders of Sex Development (DSD), as well as assessment of long-term outcome of these rare conditions, requires multicentre collaboration across national boundaries and across multiple clinical and research disciplines. Between 2008 and 2011, the DSD Registry was at the heart of the EuroDSD collaboration for supporting the sharing of data. Since 2011 the Registry has been supported through MRC as the International DSD Registry which adheres to the highest standards of data governance and security.
Results: In May 2013, there were 1129 cases added by registered users from 22 centres in 15 countries across 3 continents. A further 51 centres and 19 countries have registered as users (without cases) covering all 6 habitable continents. The age of presentation ranges from < 1 month to 53 years, with a median age of presentation of 6 months. The median year of birth is 1996 (range 1927-2012). The commonest disorder type is disorders of androgen action (327) followed by disorders of gonadal development (259). In addition to clinical data, biological samples are available in 42% (478) cases. The Registry was upgraded in 2013 and its structure is now an optional modular system for inputting clinical data. Patient information leaflets were revised and approved. These changes support development of the Registry as a resource for specific areas of interest such as CAH and Transition.
Conclusions: The I-DSD Registry is open to new researchers and clinical contributors who can register to use the Registry at www.i-dsd.org. In addition to acting as a resource for assessing clinical outcome, the I-DSD Registry is facilitating the development of a network of DSD centres and specialists. In case of queries please contact the I-DSD Project Manager, Jillian Bryce (Jillian.Bryce@glasgow.ac.uk). *The IDSD project is funded by MRC (G1100236)*

WG6-118 Disorders of Sex Development (DSD): Information and Communication in the Context of DSD

dsd-LIFE: Clinical European study on the outcome of and experiences with hormonal therapies, surgery, psychological support and psychological intervention in DSD

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dsd-LIFE is a comprehensive clinical outcome study integrating all medical and psychosocial issues to improve treatment and care of DSD. The multidisciplinary dsd-LIFE project consortium consists of 15 experienced international scientists in the areas of endocrinology, psychology, surgery, gynaecology and ethics. dsd-LIFE stands for sustainable improvement of clinical care for patients with disorders of sex development (DSD) on European level through an evaluation of different areas of high importance for life quality: HRQOL and psychological well-being, psychosexual development, surgery, hormones and metabolism, patients' view, ethics and cultural context. Patient support groups have been contacted to integrate patients views, ideas and concern for the study.The recruitment of participants will start in October 2013. It will be performed by the study centres, associated hospitals, patient support groups and I-DSD. Physicians, psychologists and nurses will receive training and standard operating procedures (SOP) to perform the study in a standardized manner in all study centres. On basis of the data received the evaluation and development of clinical guidelines is set up, thoroughly coordinated by the project national coordinators, who closely interact with the project coordinator. The results of the study will be disseminated through scientific, health care societies, patient support groups and published in correspondent journals. Moreover, dissemination of general knowledge about DSD to the public will be enhanced through the project.

DSDnet: building a network for studies of differences of sex development

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The European Cooperation in the field of Scientific and Technical Research (COST) has recently approved a proposal for an Action "DSDnet: Systematic elucidation of differences of sex development" (BM1303). This Network aims for (1) the standardisation of diagnostic and management aspects in DSD, (2) the creation of a European Reference Network of national Centres of Expertise for better accessibility and improvement of care, (3) the identification of the genetic causes of DSD and the translation of findings into novel diagnostic tools, (4) the improvement of communication and a debate on ethical and legal guidance. This COST Action will provide five working groups dealing with different aspects to achieve the aims and will work closely with the I-DSD database project. Furthermore it will create a website to communicate public information about DSD, as well as internal communication for partners. Especially young scientists are encouraged to join the DSDnet, as we aim to provide funding for short-term sceintific missions, training schools and workshops. A further aim of the action is to secure funding for both translational research and clinical studies on a world-wide scale. The Action is open to all COST countries and also will especially invite non-COST countries for participation.

Free Communications

FC1-120 Gonads and Gynaecology

Lack of expression of Gtsf1 (Gamete Specific Function 1) gene in cryptorchid boys at high risk of infertility

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Background: Recently, Gtsf1, a member of the evolutionarily conserved UPF0224 gene family involved in spermatogenesis and retrotransposon suppression, was found to be expressed predominantly in male germ cells in the adult murine testis. In has been also demonstrated that Gtsf1-null mice exhibited male-specific sterility. Furthermore, the Gtsf1-null testes showed derepression of the retrotransposons Line-1.
Objective and hypothesis: To date, there is no information in the literature about Gtsf1 expression and localization in prepubertal human testis of cryptorchid boys.
Methods: Whole genome analysis of testicular biopsies from 7 boys with typical testicular histology of a high risk infertility group (HIR) underwent orchiopexy. Samples were analyzed using Affymetrix microarrays, quantitative real time PCR and immunohistology. Results were compared to those from similar analyses of 12 biopsies from cryptorchid boys at low risk for developing infertility (LIR).
Results: GTSF1 protein was found to be localized in cytoplasm of spermatogonia in both low and high infertility risk groups. In the high infertility risk group, however, GTSF1 protein expression was lower and its cytoplasmic distribution was irregular. GTSF1 gene expression was below limit of detection seen in HIR but was strongly expressed in LIR testes [HIR log2 expression 4,6 vs 7,27 in LIR, adjusted $p < 0.0001$].
Conclusion: These results indicate that gene expression of Gtsf1 which is required for spermatogenesis and involved in retrotransposon suppression in male germ cells is impaired in cryptorchid boys at high risk of infertility and the locations of cytoplasmatic GTSF1 protein is different. Since cryptorchid boys are at high risk of intertility, these results suggest that Gtsf1 expression may contribute to the development of infertility.

FC1-121 Gonads and Gynaecology

Cryptorchidism and testicular abnormalities related to a novel correlation of gene variants of insulin-like 3 hormone (INSL3) in boys

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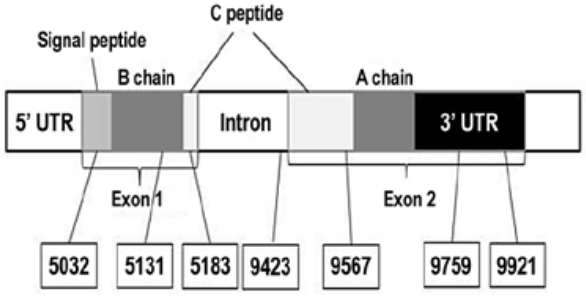
Background: Cryptorchidism is a common birth defect in males.INSL3 plays a pivotal role in testicular descent and the formation of the developing gonad. It is transcribed by 2 exons and it is composed of a signal peptide, A and B chains and a C-peptide. INSL3 single nucleotide polymorphisms(SNPs) have been described in cryptorchidism and INSL3 is also related to Polycystic Ovary Syndrome (PCOS) in women.
Objective and hypotheses: To identify possible INSL3 SNPs in boys with cryptorchidism and their possible involvement in its pathogenesis.
Methods: Genomic DNA was extracted from the blood of 43 age-matched controls and 49 boys with abdominal(AC), inguinal(IC), ectopic (EC)cryptorchidism or ascending testes(AT). The samples were sequenced for exons 1 and 2 of INSL3.
Results: Two known mutations were identified: *R102H(exon 2),* in an IC patient whose mother had PCOS, and *C9423T*(intronic), in an AT patient. Also several SNPs were identified: **(1)** at exon 1: *A9A(G5032A), L42L(A5131G)* and T60A(A5183G) and **(2)** at the 3' Untranslated Region(UTR) two SNPs: at *C9759A* and at *G9921A*. The patients showed a higher frequency for the minor allele in the genetic loci A*5131G* (52%), A*5183G* (79%) and G*9921A* (78.4%)($p \leq 0{,}011$) in comparison to the controls (36%, 61.6% and 78.7%,respectively). Furthermore, the patients with AC(62.5%, p=0,001) and EC(60%,p= 0,007) had a homozygous genotype for the minor allele at loci *A5131G, A5183G* and *G9921A* at a higher frequency than the controls(5%). Some AC patients had abnormal testes.



[Figure 1: INSL3 pro-hormone encoding regions and the identified variants]

Conclusions: The mutations *R102H* and *C9423T* of INSL3 are also associated with cryptorchidism in the Greek population. The novel homozygotic combination of the three polymorphisms *A5131G, A5183G* and *G9921A* in patients with abdominal and ectopic cryptorchidism possibly reflects a stronger phenotypic correlation of these 3 SNPs with the severity of cryptorchidism that may also be associated with structural malformations of the undescended testis.

FC1-122 Gonads and Gynaecology

Sexuality, fertility and gonadotropic axis evaluation in 191 men born with classic 21-hydroxylase deficiency (21OHD): first results of a French multicentre survey

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Since almost 10 years an increasing number of publications indicate that fertility in men born with congenital adrenal hyperplasia (CAH) due to classic 21OHD deficiency is far from normal, as initially thought.

We create a French network in order to study the consequences of the disease on sexual life, fertility, testicular functions and gonadotropic axis, in a great and representative sample of well genotyped men with CAH/21OHD. We collected relevant clinical and hormonal data from medical files and patient's responses to questionnaires concerning personal life and sexual life.

To date 191 men with a median age of 28±9 yrs (18-50) have been already included in the study from 28 different French teams. Of these patients, 73% had a salt-wasting (SW) and 27% pure virilizing forms. Mean height (m±SD) was 167±8 cm and mean BMI was 26±5 kg/m^2. A partial evaluation of couple life in Feb 2013 showed that 68% patients were living with a female partner and that 41% had children. To date 133 patients (70%) underwent testicular ultrasound and 43 (32%) had TART. Surprisingly, a sperm count was only performed in 54 (28%) of them. From these, 74% had abnormal sperm count which will be detailed. Hormonal evaluation of the testicular functions and the gonadotropic axis was performed in 160 men. Several hormonal profiles were observed (normal, gonadotrope deficiency or primary testicular insufficiency). Their mechanisms will be discussed. In theory and on the whole the patients received a mean dose of 26±13 mg of hydrocortisone/day. SW patients also received 90±75 µg/d of fludrocortisone. Very high ACTH, 17OHP levels in the majority of them indicate poor therapeutic compliance.

At the end of this program, a specific map of the centers taking care of CAH/21OHD men in France will be available. Genotype-phenotype relationship and it influence on personal life, sexuality and fertility will be established in an important series of men suffering the disease.

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FC1-123 Gonads and Gynaecology

Assisted reproductive therapies and Prader-Willi syndrome: a preliminary Italian survey

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Background: Prader-Willi syndrome (PWS) is the first human syndrome identified with genomic imprinting. Several studies indicate that assisted reproduction technologies (ART) can sometimes affect the epigenetic cycle of imprinting as well, and that this gives rise to imprinting disease syndromes. However, the magnitude of this risk in PWS remains unknown.

Objective: The aim of this study was to evaluate the frequency of ART conception in a large cohort of Italian subjects with PWS born after 1978.

Methods and patients: A nation-wide questionnaire survey was performed regarding ART in families with a subjects with PWS, including questions on fertility, parental age, pregnancy and birth.

Results: 153 PWS subjects, 85 females, aged 16.9±9.8 yrs (mean±SD) were evaluated. Eighty-seven patients had a deletion of the paternally-derived chromosome 15 (del15q11-13), 56 presented uniparental maternal disomy for chromosome 15 (UPD15), one had an imprinting defect, one had a translocation involving chromosome 15, while a positive methylation test was demonstrated in 8 subjects. Two individuals were born by ART (using IVF) (1.3%), and both had a del15q11-13. Other significant findings include:

(a) a parental age at conception of 31.1±6.1 yrs (mothers) and 34.0±6.5 yrs (fathers);

(b) an increased frequency of premature term (< 37 weeks of gestation): 21.5%;

(c) a high frequency of breech position at the time of delivery (32.3%);

(d) a high rate of cesarean section (66.6%);

(e) a high number of small-for-gestational-age birth weight: 24.2%.

Conclusions: This study did not find evidence of an association between ART and PWS. However, paternal del15q11-13 and UPD15 are the overwhelming causes of PWS, while epimutations make up only a small proportion of cases. Our results reinforce the hypothesis that the association between ART and imprinting disorders, such as Beckwith-Wiedemann syndrome, is because of a specific link to loss of methylation at a critical imprinting control region.

FC1-124 Gonads and Gynaecology

Preliminary results of the fertility preservation in a group of Klinefelter adolescents

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Background: Klinefelter Syndrome (KS), is the most common sex chromosomal abnormalities (1/600 newborn males), and is characterized by hypergonadism hypogonadism. Until few years ago, mostly non-mosaic KS was considered as a model of complete male infertility although few KS (4-8%) have an oligospermia. Recent studies in adults with non-mosaic KS reported the possibility of sperm retrieval by testicular biopsy (TESE) in around 50% cases and some pregnancies have been obtain after TESE with Intracytoplasmic

Sperm Injection (ICSI). Since 1997, one hundred births are described.
Objective and hypothesis: As some studies shown a decrease of successful sperm retrieval with the increasing of age, we have plan to compare the potential of sperm retrieval between two groups "adult" (23-55 years) and "young" after the onset of puberty (15-22 years). We report our preliminary results on sperm retrieval in the ejaculate and TESE in non-mosaic KS.
Population and methods: From September 2010 to march 2013, 38 men KS non-mosaic (without androgen therapy since 6 months) have been included: 12 in the "adult" group and 26 in the "young" group. After clinical and biological evaluation, two seminal analysis spaced out 3 months was performed followed by a TESE if sperm retrieval in ejaculate was negative.
Results: The mean age (min-max) was 30y (24-39) for the "adult" and 19.7y (15-22) for the "young". No significant difference between the two groups has been observed for testicular size, reproductive hormones. No patient in each group had sperm retrieval in ejaculate. TESE was successfully in 4 of 6 cases (66.6%) for the "adult" and in 9 of 13 cases (69.2%) for the "young".
Conclusions: Close to onset of puberty, men with non-mosaic KS could cryopreserve sperm from testicular biopsy. These preliminary results must be confirmed for an optimization of the fertility preservation. Further studies are necessary to demonstrate if the quality of the sperm retrieved in the "young" group is better.

FC1-125 Gonads and Gynaecology

Genome-wide methylation analysis in Klinefelter syndrome

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Background: Epigenetic changes such as DNA methylation have been proposed to play a role in human disorders such as psychiatric diseases, autoimmune diseases and metabolic diseases like obesity and diabetes. Klinefelter syndrome (KS) is associated with an increase risk of these disorders, however no study to date has investigated global methylation changes in patients with KS. The aim of this study was to investigate whether KS is associated with differentially methylated genes which might have impact on the KS phenotype.
Objective and hypotheses: To examine the global methylation pattern in KS. We hypothesize that the methylation pattern is changed in KS and that the methylome changes possibly will explain phenotypic characteristics present in KS.
Methods: We performed genome-wide DNA methylation analysis on blood leucocytes from 73 patients with KS and 73 age- and gender-matched controls using the Illumina Infinium Human Methylation 450K BeadChip.
Results: 70.525 CpG-sites covering over 15.000 genes were found to be differentially methylated in patients with KS compared to the age-matched controls. Among these 61.567 were on autosomal chromosomes, 8903 were on the X-chromosome and 55 were on Y-chromosome. One of the genes with promotor associated differentially methylated CpG sites is the NSD1 gene which is involved in the androgen receptor (AR) transactivation. Other genes possibly involved in the phenotype of KS and differentially methylated were ABI3BP, APOB, C1orf59, CACYBP, DPPA5, GABRG1, HOXA4, LRRC61, NLRP2, PEX10, RPLP1, RFPL2, SDHAF1, SPEG.
Conclusions: For the first time we show that KS is associated with pervasive genome-wide methylation changes, changes which could play a role in the clinical phenotype seen with KS.

FC2-126 Bone and Growth Plate

IGF-1 signaling is essential for differentiation of mesenchymal stem cells for peak bone mass

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Background: Survival of children with chronic medical illnesses is leading to an increase in secondary osteoporosis due to impaired peak bone mass (PBM). Insulin-like growth factor type 1 (IGF-1) levels correlate with the pattern of bone mass accrual and many chronic illnesses are associated with low IGF-1 levels. Reduced serum levels of IGF-1 minimally affect the integrity of the skeleton, whereas recent studies suggest that skeletal IGF-I regulates PBM.
Objective and hypotheses: To determine the role of local IGF-1 in postnatal bone mass accrual.
Methods: We established an inducible type 1 Igf receptor *Cre/lox* knockout mouse model, in which the type 1 Igf receptor was deleted inducibly in mesenchymal stem cells (MSCs) from 3-7 weeks of age.
Results: The size of the mouse was not affected as knockout and wild type mice had similar body weights and nasoanal and femoral lengths. However, bone volume and trabecular bone thickness were decreased in the secondary spongiosa of female knockout mice relative to wild type controls, indicating that local IGF-1 is critical for maintenance of bone mass. IGF-1 signaling in MSCs in vitro has been implicated to be involved in both migration to the bone surface and differentiation into bone forming osteoblasts. To clarify the exact role of IGF-1 in bone, we found by immunohistochemical analysis that a similar number of Osterix-positive osteoprogenitors were on the bone perimeter, indicating migration of MSCs was not affected. Most importantly, 56% fewer osteocalcin-positive mature osteoblasts were present on the bone perimeter in the secondary spongiosa in knockout mice versus wild type controls.
Conclusions: These in vivo data demonstrate that the primary role of skeletal IGF-1 is for the terminal differentiation of osteoprogenitors, but refute the role of IGF-1 in MSC migration in vivo. Additionally, these findings confirm that impaired IGF-1 signaling in bone MSCs is sufficient to impair bone mass acquisition.

FC2-127 Bone and Growth Plate

Evidence that estrogen hastens epiphyseal fusion and cessation of longitudinal bone growth by irreversibly depleting the number of resting zone progenitor cells

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Background: With age, growth plate cartilage undergoes functional and structural senescence, eventually causing epiphyseal fusion and cessation of bone elongation. Estrogen accelerates this process.
Hypothesis: Senescence occurs because progenitor cells in the resting zone are depleted in number and/or replicative capacity, and estrogen accelerates this depletion.
Methods: 11-week-old ovariectomized rabbits received estradiol cypionate (70 mcg/week) in oil or vehicle intramuscularly for 5 weeks[BJ([1] and then were left untreated for an additional 5 weeks.
Results: During treatment, estrogen accelerated the normal decline in growth rate ($P < 0.001$), proliferation rate ($P < 0.001$), growth plate height ($P < 0.001$), number of proliferative ($P < 0.001$), and hypertrophic chondrocytes ($P < 0.001$) (all consistent with prior studies) and also in the number of resting zone chondrocytes ($P < 0.001$). Five weeks after stopping treatment, animals that had received estrogen continued to show advanced structural senescent changes, including advanced decline in growth plate height ($P < 0.001$), number of resting ($P < 0.001$), proliferative ($P < 0.001$), and hypertrophic chondrocytes ($P < 0.001$). Estrogen-treated animals also underwent earlier growth plate fusion ($P < 0.001$). However, the estrogen-induced decrease in chondrocyte proliferation and growth rate recovered after estrogen treatment was stopped.
Conclusions: Estrogen irreversibly accelerates the decline in the number of resting zone chondrocytes. In addition, estrogen suppresses proliferation in

the proliferative zone, but this suppression reverses after cessation of estrogen treatment, suggesting that it does not reflect proliferative exhaustion. Thus the findings indicate that estrogen hastens epiphyseal fusion and the cessation of linear growth primarily by depleting the number of resting zone progenitor cells rather than their proliferative capacity.

FC2-128 Bone and Growth Plate

Patients with mutations in PHEX or FGF23 share FGF23 excess but present distinct bone and mineral metabolism features

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Background: X-linked hypophosphatemic rickets (XLHR),due to loss of function mutations in the endopeptidase PHEX,is the most frequent form of HR with elevated FGF23. PHEX is expressed by osteoblasts,osteocytes and odontoblasts; its precise function in controlling circulating FGF23 level is still unclear. FGF23,secreted by osteoblasts and osteocytes regulates phosphate handling and vitamin D metabolism mainly through its action on kidney. Specific missense mutations of FGF23 prevent FGF23 cleavage and inactivation, and thus result in the rare autosomal dominant form of HR (ADHR) with elevated circulating FGF23.
Objective: Examine the role of PHEX on bone and mineral metabolism by comparing the phenotype of patients with high FGF23 and HR due to PHEX or FGF23 mutations.
Methods: 6 patients with FGF23 mutations and ADHR (4 children and 2 untreated adults). 23 patients with PHEX mutations and XLHR (18 children and 5 untreated adults).
Results: Children with FGF23 mutations were diagnosed earlier (1.5±0.0 yrs) than children with PHEX mutations (2.3±0.2 yrs, p=0.03),with similar leg bowing (intercondylar distance 7.9±2.3 and 5.0±0 .7, p< 0,005). At diagnosis, ADHR patients presented with bone demineralization and fractures in one patient,whereas none of the 18 XLHR patients had bone demineralization or fractures. In addition, ADHR patients had significantly higher alkaline phosphatases than XLHR patients (2037±439 and 649±103, p=0.01, respectively). Patients follow up revealed that, in opposition to XLHR, treatment easily restored serum phosphate levels in ADHR; final height of untreated ADHR adults appears higher (-1,2 and -1 SD) than that of untreated XLHR (-3,2±1,4 SD).
Conclusions: Despite the limited number of patients, we pinpointed differences in the phenotypes of ADHR and XLHR. This suggests that the phenotype associated with PHEX deficiency does not uniquely result from FGF23 excess, yet advocates for a direct role of PHEX on bone mineralization and growth.

FC2-129 Bone and Growth Plate

Neuroradiologic and neurophysiologic study of the cranio-cervical junction in children affected by achondroplasia

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Background: Achondroplasia is characterized by severe disarmonic short stature.Typical is the narrowing of the foramen magnum, which can determine, especially during the first years of age, a compression of the cervical medulla and a myelomalacic damage.It is debated whether to periodically perform magnetic resonance imaging (MRI) of the cranio-cervical junction in asymptomatic children. Few studies have focused on the use of somatosensory evoked potentials of the upper limbs (SSEP-UL). Different opinions are stated on the decision to undergo a surgical decompression procedure in asymptomatic patients with neuroradiologic pathologic findings.
Objective and population: To compare the utility of MRI and SSEP-UL in 20 affected young children (under 6 years of age) for the diagnosis of intramedullary alterations and for the follow-up in 6 patients who underwent surgical decompression of the foramen magnum.
Results: We noticed a significant hyperintense signal in T2 sequences of the cranio-cervical MRI in 35% of the patients.We demonstrated a lower sensitivity of the SSEP-UL (40%) compared to the MRI. However, a very high specificity of the SSEP-UL (100%) was observed.Six patients underwent surgical decompression of the foramen magnum. Five among them showed pre-operative alterations in the MRI study, only three of them had pathologic SSEP-UL. A normalization of the pathologic SSEP-UL and a partial remission of the altered MRI images demonstrated the efficacy of the surgical procedure.
Conclusions: This is the first multidisciplinary study in literature which focuses exclusively on young affected children. The data collected underlines the importance of a neuroradiologic follow-up during the first years of age. MRI seems to be the best tool to evaluate the cranio-cervical junction, while SSEP-UL can be useful in asymptomatic patients with MRI alterations to confirm a functional damage and to prevent the appearance of more severe neurological manifestations.

FC2-130 Bone and Growth Plate

High spontaneous osteoclastogenesis in paediatric osteogenesis imperfecta patients receiving and not receiving intravenous neridronate

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Background: Osteogenesis imperfecta (OI) is a heritable disease of the connective tissues caused primarily by heterogeneous mutations in the genes encoding for type I collagen. Phenotypically, it is characterized by abnormal bone mineralization, tissue fragility, and skeletal deformities. Objective. The aim of this study was to investigate the osteoclastogenic potential of unfractionated peripheral blood mononuclear cells (PBMCs) from OI patients (mean age 10.44 ± 3.48) who received cyclical neridronate infusions for at least 1 year, untreated OI patients and control subjects.
Methods: PBMCs from 6 patients and 6 controls were cultured in presence/absence of M-CSF and RANKL. At the end of the culture period, mature multinucleated OCs were identified as TRAP+ cells. By real-time PCR we studied gene expression in freshly isolated PBMC. By flow cytometry we

characterized the presence of OC precursors (CD14+/CD16+) and we studied TNF-alpha expression.
Results: Spontaneous formation of osteoclasts, without adding M-CSF and RANKL, occurred in PBMC cultures from treated and untreated OI patients. In these patients, the percentage of circulating osteoclast precursors, CD14+/CD16+ cells, increased respect to the controls (12.5% vs 0.1%, $p< 0.01$). By real time PCR, we found high levels of RANKL, TNF-alpha and MCSF receptor, as well as decreased OPG levels, thus leading to the increase of RANKL/OPG ratio. High TNF-alpha levels were also found on monocytes through flow cytometry.
Conclusion: We showed for the first time the high osteoclastogenic potential of PBMCs from young OI patients, treated and untreated with bisphosphonate, which could be due to the high percentage of circulating OC precursors, to the elevated TNF-alpha levels as well as to the increased RANKL/OPG ratio. This condition could contribute to the bone disease affecting these patients.

FC2-131 Bone and Growth Plate

Adult Prader-Willi patients have smaller and weaker bones

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Background: Obesity has been considered to yield a protective effect against the risk of fractures in adults, however recently, fat mass has been shown to be inversely associated with BMD and apparently to be detrimental for the bone.
Objective and hypotheses: To evaluate bone geometry and strength in a group of adult obese patients with Prader Willi(PW) syndrome and to evaluate the modulating effect on bone of GH therapy.
Methods: This was a cross sectional observational study performed in 41 (26 males, 18 females) obese subjects with genetically confirmed PW, aged 29.4 ± 8.6 years. Mean height was 153.1±8.2 cm and BMI 41.4±11.3 kg/m². Twenty three of the patients were on GH treatment for a mean period of 6.2±3.1 years. Twenty two subjects of normal height and weight served as controls. Bone geometry was evaluated at metacarpal level as: outer diameter (D), inner diameter (d), cross sectional area (CSA), cortical area (CA), medullary area (MA), metacarpal index (MI) and bone strength (BBRI), according to the formula $[D^4 - d^4 / D]$.
Results: D, CSA, MI, CA and BBRI were significantly lower than in controls, but not medullary area.

	n	D	d	MI	CSA	CA	MA	BBRI
PW	41	7.6 ±0.7	3.6 ±0.8	0.5 ±0.1	183.1 ±36.4	34.8 ±6.8	10.9 ±4.6	422.9 ±123.3
Controls	22	8.6 ±0.9	3.3 ±1.1	0.6 ±0.1	235.8 ±51.6	49.6 ±11.2	9.3 ±5.7	641.2 ±200.3
p		0.000	NS	0.000	0.000	0.000	NS	0.000

[Bone geometry and bone strength of PW and controls]

Data are mean ± SD
GH treatment has a positive effect on the periostal growth (D, CSA, CA) and also on the medullary one (d, MA) and on bone strength (BBRI).
Conclusions: Obese PW patients have smaller bones with normal medullary area resulting therefore in a thinner cortical area and weakness leading eventually to fractures. GH treatment seems to partially rescue this picture, allowing a bone expansion. Altogether, since oestrogens are known to inhibit periosteal bone apposition and stimulate endocortical bone formation our findings in PW patients seem to be just a consequence of an enhanced aromatase activity secondary to the enlarged fat mass.

FC3-132 Growth

An activating mutation of the natriuretic peptide receptor 2 causes extremely tall stature

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Background: C-type natriuretic peptide (CNP)/natriuretic peptide receptor 2 (NPR2) signalling is essential for long bone growth. In response to CNP binding, NPR2 synthesises cGMP, which stimulates proliferation, growth and differentiation of chondrocytes. Enhanced CNP production caused by chromosomal translocations results in tall stature, a Marfanoid phenotype and skeletal abnormalities. A similar phenotype was described in a family with an activating *NPR2* mutation in the guanylate cyclase domain.
Case: Here we describe an extremely tall male without skeletal deformities, with a novel *NPR2* mutation (p.Arg655Cys) in the kinase homology domain (KHD).
Objectives: To investigate the functional and structural effects of the *NPR2* mutation.
Methods: We performed site-directed mutagenesis and transfected wildtype and mutant NPR2 into HEK293 cells for guanylate cyclase assays and co-immunoprecipitation. Patient skin fibroblasts were also used for guanylate cyclase assays. We performed homology modelling to understand the molecular mechanism by which the mutation influences NPR2 function.
Results: CNP stimulated cGMP production of the mutant NPR2 was markedly increased in patient skin fibroblasts and in transfected HEK293 cells. The stimulatory effects of ATP on CNP-dependent guanylate cyclase activity were augmented, suggesting that this novel mutation enhances both the responsiveness of NPR2 to CNP and its allosteric modulation/stabilisation by ATP. Co-immunoprecipitation showed that wildtype and mutant NPR2 can form stable heterodimers, suggesting a dominant positive effect. In accordance with augmented endogenous receptor activity, plasma NTproCNP (a marker of CNP production in tissues) was reduced in the patient.
Conclusions: We report the first activating mutation within the KHD of *NPR2*, which results in extremely tall stature, emphasising the important role of this domain in the regulation of guanylate cyclase activity and bone growth in response to CNP.

FC3-133 Growth

Excess mortality in children born short

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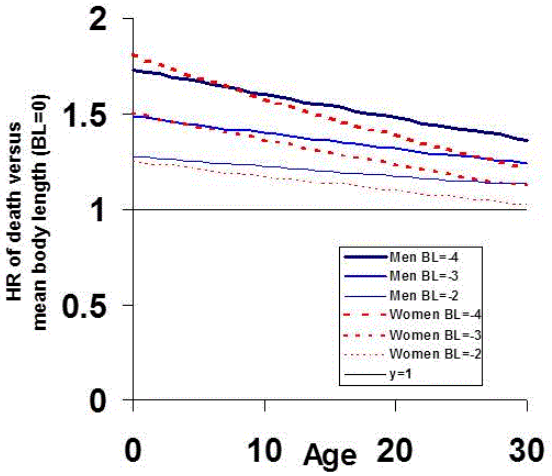
Background: Concerns have been raised about increased long-term mortality in children born small for gestational age (SGA).
Objective and hypotheses: The objective was to study the impact of length at birth on mortality rate later in life.
Methods: General population data were retrieved from the Swedish Medical Birth Registry and Congenital Malformations Registry (1973-2010): 1.880.668 males, 1.781.133 females and the Cause of Death Registry (1985-2010), with 28.026 deaths, 17.390 males and 10.636 women. Main outcome measures were hazard ratios of death. Estimation of male and female continuous hazard functions of death was performed using Poisson regression. The model included interaction between length at birth and chronological age.
Results: There was a substantial excess mortality among children short at birth still at the age of 10 and older, see Figure. At the age of 10, those with birth length $_{SDS}$ -2 had 22% (boys) and 17% (girls) higher risk than those with normal length at birth. If birth length $_{SDS}$ was -3 the excess risks are 40% and 30%, respectively, for men and women.
Conclusion: Children born short have a long term ~ 20% increased mortality rate in spite of the fact that a large proportion ~ 90% will show postnatal catch up growth. Whether the excess mortality is present mainly in the subgroup which remains short needs to be further studied.



[Figure 1: The hazard ratios of death versus the risk when BL=0 depending on the gestational age adjusted SD score of length at birth. When BL is -2 or less the excess mortality is around 20% or more during a long period of childhood and youth.]

FC3-134 Growth

Heterozygous mutations in natriuretic peptide receptor-B gene *(NPR2)* as a cause of idiopathic short stature

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Background: The C-type natriuretic peptide (CNP) and its receptor (NPR-B) system has emerged as an important regulator of endochondral bone growth. Homozygous loss-of-function mutations in the NPR-B gene (*NPR2)* cause acromesomelic dysplasia, type Maroteaux (AMDM), a skeletal dysplasia with extreme short stature. Heterozygous relatives had short stature.
Objective and hypotheses: To investigate the presence of *NPR2* mutations in a group of patients with idiopathic short stature (ISS) and determine their phenotypic features.
Methods: The *NPR2* coding region was directly sequenced in 47 independent patients with ISS. The functional consequences of *NPR2* non-synonymous variations were established using in vitro cell-based assays. To evaluate guanylyl cyclase activity, we examined cGMP production by CNP treatment in the COS7 cells transfected with either wild type or mutant constructs.
Results: Three novel heterozygous *NPR2* mutations were identified (6.4%): c.226T>C p.Ser76Pro (patient 1), c.788G>C p.Arg263Pro (patient 2) and c.2455C>T p.Arg819Cys (patient 3). All of them predict amino acid changes in highly conserved residues in NPR-B. None of these allelic variants were found in 116 alleles from controls. These mutations segregated with short stature phenotype in an autosomal dominant pattern (Height SDS ranged from -4.5 to -2.1). Defects in *SHOX* gene were ruled out. One of these patients has disproportionate short stature (sitting height:height SDS = +2.3), whereas in another patient, conical and shortened epiphyses were observed. All these 3 patients were treated with rhGH (33-50 µg/kg/d) with poor response. Functional studies revealed no cGMP responses by cGMP assay.
Conclusions: We identified heterozygous NPR2 mutations leading to impaired guanylyl cyclase activity in vitro in 6% of patients with ISS in the present cohort. It is important to establish NPR2 mutations as a common cause of ISS because it could affect future diagnostic or treatment opportunities.

FC3-135 Growth

The physiological role of circulating and breast milk adiponectin and leptin in infancy growth

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Background: Adiponectin (ADPN) regulates insulin sensitivity. Lower circulating levels are found in children with greater adiposity, and in SGA infants showing rapid weight gain. Leptin correlates with childhood adiposity.
Objective: To explore relationships between human breast milk (HM) and infant dried blood spot (DBS) ADPN & leptin levels, and infancy growth, in non-SGA infants, where few previous studies exist.
Method: Samples were obtained from a large cohort, with detailed infancy anthropometry. 3-month (3m) DBS, and a subgroup at 12 months (12m), were processed using ADPN & leptin immunoassays. HM hindmilk samples were collected at 4-8 wks postnatally, and HM adipokines measured by radioimmunoassay.
Results: Mean±SD ADPN was higher at 3m in 307 non-SGA infants (143 male) [13.3±4.9 (4.1-32.1)ug/ml] than at 12m (N=63) [4.4±1.6 (1.5-9.0)ug/ml]. Among 3m samples, ADPN was inversely related to exact age (B -0.1,p< 0.0005).
Infant nutrition: 3m ADPN was higher in exclusively breast-fed vs mixed or formula-fed infants (p=0.01), independent of body size, and positively related

to HM ADPN [27.8±7.1ng/ml (N=631)]. In contrast 3m leptin was unrelated to nutrition type or HM leptin [5.2±8.9 (0.0-73.2)ng/ml].
Infant growth: 3m ADPN was inversely related to birth-weight, length and skinfold thickness, and 3m weight and length. In age-adjusted multivariate models the strongest determinant of 3m ADPN was length. 3m leptin [2.9±2.1 (0.6-20.0)ug/ml] was positively related to body size & adiposity. Neither HM adipokines correlated with infancy growth.
Conclusions: Circulating ADPN & leptin were quantified from DBS by immunoassay, and showed divergent associations with body size. ADPN levels were higher in smaller, shorter infants, declined with age and were nutritionally regulated. In contrast, leptin was positively associated with adiposity. HM adipokines were not associated with growth.

FC3-136 Growth

Trajectory analysis - a method to show growth patterns proceeding to obesity in children

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Background: Obese children will often be obese adults with increased risk to cardiometabolic diseases. Adiposity rebound (AR) occurring at earlier age than usual has also been shown to increase the risk of obesity.
Objective: The aim of the present study was to longitudinally analyze the BMI of children.
Methods: The study consists of growth data from birth and at 0.5, 1, 2, 5, 7, 12, and 15 years of age of children born 1974 (n=1108), 1981 (n=977), 1991 (n=586) and 1995 (n=786) and of birth cohort 2001 (n=766) until the age of 11 years. The data was analyzed with trajectory analysis grouping children with similar growth into their own groups, trajectories.
Results: Two abnormal growth trajectories were established in the longitudinal data of 4 223 children. The trajectory proceeding to overweight reached a higher BMI level already during the first year of life. The number of children at this trajectory increased from 17.5% in the birth cohort of 1974 to 25.3% in the cohort born 1995. The other abnormal trajectory showed how children born small for gestational age grew fast in infancy and accelerated weight gain continued during preschool age reaching the 50th percentile BMI curve by the age of 15 years. From the children studied, 7% belonged to this group. In 2000''s the AR occurred 0.8 years earlier compared to 1970''s (1974 5,8yrs and 2001 5,0yrs). The age for AR was clearly lower in large children (4,2 yrs), and also in children born small for gestational age (5,5yrs) compared to children of the other two groups (5,6yrs and 6,3yrs). In addition, the age during the first year of life when the BMI reached it''s highest level diminished from 12.2 months in 1974 to 9.3 months in 2001.
Conclusions: Trajectory analysis is a a useful method to analyze longitudinal growth data in childhood. Recognizing abnormal growth trajectories early in life might predict future health risks and could help to focus family oriented life counseling.

FC3-137 Growth

Bone age assessment by a novel quantitative ultrasound based device, SonicBone, is comparable to the conventional Greulich and Pyle method

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Background: Bone age (BA) assessment in children is based on the interpretation of hand x-ray scans according to Greulich and Pyle standard atlas (GP). The aim of the study was to evaluate an ultrasound based device, SonicBone, for safety, reproducibility and concordance to the current method.
Methods: Study population included 150 participants, 74 males, mean age 10.6±3.3 years, attending pediatric endocrinology clinic. X-ray scans were evaluated independently by 4 pediatric endocrinologists according to GP. SonicBone assessments were performed by two observers. Study population was randomly divided to 2 groups. A group of 100 participants, to assess correlation between speed of sound (SOS) and distance (DIS) parameters of SonicBone and BA by GP, and to establish an algorithm for provision of a numeric BA assessment in years. A group of 50 participants to assess concordance between BA based on GP and BA based on SonicBone.
Results: The SonicBone has high repeatability performance, 0.73% relative standard deviation (RDS) for SOS and 3.5% RDS for DIS. Pearson correlation between BA by GP, SOS and DIS demonstrated a significantly high correlation in all areas. The algorithm including age, gender, SOS and DIS for each skeletal location, wrist, carpal and phalangeal, has R square of 0.87, $p < 0.004$. BA by SonicBone was highly correlated with BA by GP, with R square of > 0.946 and p value < 0.0001 for all locations.
Conclusion: SonicBone device is safe, portable, non painful, radiation free and highly reproducible. Its BA assessment in a population of children attending pediatric endocrinology clinics is comparable to BA by GP method.

FC4-138 Puberty

Loss-of-function mutations in a gene cause central precocious puberty

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Background: The onset of puberty is primarily detected by an increased pulsatile secretion of gonadotropin-releasing hormone (GnRH). To date, only few and rare molecular defects were associated with the phenotype of central precocious puberty (CPP).
Objective and hypotheses: To investigate a new genetic cause of CPP using whole exome sequencing.
Methods: We performed whole exome sequencing (Illumina HiSeq 2000 platform) of 40 individuals from 15 families with CPP, including 32 affected individuals and 8 unaffected relatives. All of them had typical clinical and hormonal features of CPP, including early pubertal signs, such as breast development/ testicular enlargement and pubic hair, advanced linear growth and bone age, elevated basal and/or GnRH-stimulated LH levels and normal CNS MRI.
Results: We first analyzed exome sequence data from a total of 15 individuals in the 3 largest families with pedigrees consistent with a dominant mode of inheritance. We identified heterozygous nonsynonymous variants that were present in affected individuals and not present in unaffected family members. Given the rarity of presentation of familial precocious puberty, we excluded all variants with a minor allele frequency > 0.01% in gene databases. A shared candidate gene was identified in two of the families. Two families had novel frameshift mutation variants in this gene resulting in premature stop codons. We then examined an additional 25 subjects' exome data from 12 other families and found another novel frameshift mutation in the candidate gene present in two additional families as well as a novel missense variant present in a third family. All variants were confirmed by Sanger sequencing. Additionally, we investigated this gene in 82 apparently sporadic cases of CPP and three other frameshift mutations were detected (3.6%).
Conclusions: These findings provide very strong evidence that loss-of-function mutations in a gene detected by whole exome sequencing lead to CPP in humans.

FC4-139 Puberty

The diagnostic value of first-voided urinary LH compared with GnRH-stimulated gonadotropins in differentiating slowly-progressive from rapidly progressive-precocious puberty in girls

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Background: Characterization of pubertal progression is required to prevent unnecessary intervention in unsustained or slowly-progressive (SP) precocious puberty (PP), while delivering hormonal suppression in rapidly-progressive (RP) PP. GnRH stimulation is the gold-standard test for diagnosing PP, whereas first-voided urinary LH (ULH) was suggested as a non-invasive methods, assuming that it reflects the nocturnal arousal of LH peaks at the onset of puberty.
Objective and hypotheses: We aimed to assess the diagnostic value of ULH compared with GnRH-stimulated gonadotropins in differentiating SP-PP from RP-PP.
Methods: 62 girls with PP underwent both GnRH stimulation and ULH assay. Fifteen girls with peak LH>10 IU/L (*i.e.* advanced puberty) started treatment immediately whereas other 47 girls were evaluated after 6 months for pubertal advancement, height acceleration and bone-age progression. Based on these criteria, the participants were assigned to 5 subgroups: pubertal regression, no progression, or progression by one, two or three criteria. The first 3 subgroups were defines as SP-PP (n=29) while the other subgroups (including advanced puberty) were defined as RP-PP (n=33). Additional 23 prepubertal girls were evaluated for ULH.
Results: ULH but not serum gonadotropins could distinguish girls with 2 and 3 criteria from less progressive subgroups. By comparison to SP-PP, those with RP-PP had higher basal (0.81±1.43 *vs.* 0.12±0.05 IU/L; p=0.003) and peak LH (10.90±10.09 *vs.* 2.78±1.78 IU/L; p< 0.001), basal FSH (2.60±2.07 *vs.*1.17±0.89; P< 0.001), peak LH/FSH ratio (0.98±0.76 *vs.* 0.22±0.12; p< 0.001) and ULH (2.68±1.83 *vs.* 1.05±0.26 IU/L; p< 0.001). Based on ROC analysis, a ULH cutoff of 1.15 IU/L has a better sensitivity (91%) and negative predictive value (PV) (88%) than other parameters, with a specificity and positive PV of 72% and 79%, respectively.
Conclusions: ULH assay is a non-invasive, reliable method that can assist in the distinction between SP and RP-PP.

FC4-140 Puberty

Treated and untreated women with idiopathic precocious puberty in the 3rd and 4th decades: long-term follow-up and reproductive outcome

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Background: Central precocious puberty (CPP) may have physiological and psychological implications in adulthood.
Objective: To assess the reproductive function and psychosocial adjustment of gonadotropin-suppressive-treated and untreated CPP women in the 3rd and 4th decade of life.
Methods: Prospective historical cohort study of 214 CPP women aged 25-56 years: 135 GnRHa-treated, 18 CyA-treated, 61 untreated; control group-446 women with normal puberty from the hospital staff, matched for age and year of birth. Demographic data and gynecological status were recorded by researchers in a structured phone interview (study group) and a face-to-face interview (controls).
Results: Median time to interview from endocrine discharge was 17.1 years (12.5-35.6). PCOS was more frequent in CPP women than in controls: GnRHa-treated 29.6% vs. 17.4% (p=0.006), CyA-treated 50% vs. 20.4% (p=0.04), untreated 35.4% vs. 17.2% (p=0.0003), with no significant difference between CPP groups. Spontaneous pregnancy was similarly achieved by treated-CPP and controls: GnRHa-treated 90.4% vs. 93.4%, CyA-treated 86.7% vs. 90.2%. Assisted fertilization rate was significantly higher in untreated-CPP than treated-CPP groups (p=0.006) and controls (p=0.03). The only parameter associated with PCOS and fertility problems was untreated CPP (OR= 2.04, 95% CI, 1.0-4.16, p=0.07 and OR= 3.40, 95% CI, 1.15-10.0, p=0.047, respectively). Course of pregnancy was uneventful in 90.2% of CPP women and 90.9% of controls. Marital status, education, pregnancy rate, and number of children were similar in CPP women and controls.
Conclusions: The increased rate of PCOS among CPP women implies that the underlying neuroendocrine dysfunction persists into adult life and predisposes to reproductive disorders. Gonadotropin-suppressive therapy may have a protective effect as fertility problems were more prevalent only among untreated-CPP women. Educational achievements and social adaptation in adulthood were unaffected by CPP.

FC4-141 Puberty

Novel genes underlying pubertal delay

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Background: Studies estimate that 60-80% of variation in the timing of puberty is genetically determined, but the majority of these genetic factors remain elusive. Recently, a large genome-wide association study (GWAS) meta-analysis identified 42 loci for age-at-menarche (AAM). Additionally, more than 20 rare, high-impact alleles involved in the development and regulation of the hypothalamic-pituitary-gonadal axis have been identified in patients with hypogonadotrophic hypogonadism (HH).
CDGP represents an extreme variant of normal pubertal timing that clusters in families and segregates in an autosomal dominant pattern, suggesting that inheritance is conferred by a small number of genes.
Objective and hypotheses: To identify genetic variants responsible for Familial CDGP and ascertain their role(s) in the timing of pubertal onset. Our CDGP cohort is maximized for a homogeneous genetic composition and enriched for high- or moderate-effect alleles that are amenable to discovery through whole exome sequencing (WES).
Methods: We selected 7 very informative CDGP families, accurately phenotyped through long-term growth data for WES (52 individuals). Over 2 million variants returned were filtered and annotated through our novel bioinformatics pipeline.
Results: One novel variant in a gene known to be causal in HH was identified by this methodology. Five top-ranking candidates were identified from our bioinformatics pipieline. Nine further candidate variants were identified which lie in linkage disequilibrium with the 42 GWAS loci for AAM. Targeted resequencing of these 15 genes is underway in a further 288 CDGP individuals for validation.
Conclusions: Our results identify several new putative causal genes underlying CDGP, but also highlight significant heterogeneity in the genetic basis of pubertal delay. We demonstrate the use of a novel bioinformatics pipeline to help overcome the difficulties of causal variant identification via next-generation sequencing.

FC4-142 Puberty

Novel rare variants in *POLR3A* and *POLR3B* genes identified in 4H syndrome patients with and without isolated hypogonadotropic hypogonadism

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Background: 4H syndrome is characterized by hypomyelination, hypogonadotropic hypogonadism, and hypodontia and was recently associated with biallelic mutations in *POLR3A* and *POLR3B* genes. Congenital isolated hypogonadotropic hypogonadism (IHH) might represent a milder phenotypic variant of 4H syndrome.
Objective: To investigate *POLR3A* and *POLR3B* allelic variants in patients with 4H syndrome and IHH.

Methods: Seven 4H syndrome patients (5 males) with variable degrees of cognitive impairment and motor dysfunction were selected. Two patients had normal development; one had confirmed IHH and four males were pre-pubertal, (range 10 - 16 yrs). Twenty four IHH patients (10 normosmic and 14 Kallmann syndrome) were also evaluated in a pilot study. Mutations in the known IHH genes had been previously excluded. The coding region of *POLR3A* and *POLR3B* were analyzed by Sanger sequencing in the 4H syndrome patients. Only POLR3A was studied in IHH patients.
Results: One 4H syndrome female with IHH harbored compound heterozygous mutations in *POLR3A* (p.Ile34fs+p.Met852Val). One pre-pubertal 4H syndrome boy carried a heterozygous mutation in *POLR3A* (p.Ile952Val) and *POLR3B* (p.Thr862fs). Heterozygous *POLR3A* (p.Gln465* and p.His1286Gln) and *POLR3B* (p.Gln249*) variants were identified in 3 other 4H syndrome patients. No mutations were identified in the remaining two cases of 4H syndrome neither in the pilot IHH group. *In silico* analysis suggested that all allelic variants are deleterious, except for the p.Ile952Val. All variants were absent in the 1000 genome database.
Conclusions: Mutations in *POLR3A* and/or *POLR3B* were identified in 71% of 4H syndrome cases, although in heterozygous state in the majority of them, and were more common in *POLR3A* than in *POLR3B*. Further studies with a larger number of patients are necessary to confirm if *POLR3A* and *POLR3B* variants can be associated with congenital IHH, without other typical features of 4H syndrome.

FC4-143 Puberty

Study of gender identity disorder in children and adolescents

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Background: Childhood/adolescent Gender Identity Disorder (GID) is associated with significant distress, particularly with puberty. There is much controversy internationally over its management, including the optimal timing of hormonal treatment.
Objective and hypotheses: There has been no formal epidemiological study of childhood/adolescent GID. We examine the incidence, clinical presentation and management of GID in UK and Irish children and adolescents.
Study population: Children/adolescents aged 4-15.9 years in the UK and Republic of Ireland.
Design: Joint British Paediatric Surveillance Unit (BPSU) and Child and Adolescent Psychiatry Surveillance System (CAPSS) study. New cases of GID reported by clinicians over a 19-month period (01-Nov-2011 to 01-June-2013) are validated against the authoritative DSM-IV-TR (2000). Exclusions include disorders of sexual differentiation and major psychosis.
Primary outcome: Incidence of childhood/adolescent GID, using denominator data from the UK Office of National Statistics and the Central Statistics Office in Ireland.
Statistical analysis: Descriptive statistics and comparisons using two-sample t-tests/Mann-Whitney U tests for continuous data and Chi-squared/Fisher's exact tests for categorical data.
Results: Preliminary descriptive data from eleven months' surveillance (n=105 cases excluding duplicates, 56 males) indicate that similar numbers of males/females are affected. There is a lag of several years between median [inter-quartile range] onset of symptoms (6y [3-11y]) and presentation to Paediatricians/Psychiatrists (14y [11.4-15.1y]), with high levels of psychiatric co-morbidity and previous self-harm (in 33%) at presentation.
Conclusions: We present the first ever population-level data on the clinical features and presentation of childhood/adolescent GID. These data will inform service provision and clinical management, including the highly controversial debate around early pubertal suppression in this group.

FC5-144 Programming and Epigenetics

Paternal trans-generational effects of weaning age on maturational tempo-related gene expression in the newborn rat liver

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Context: We have shown (ESPE12) that weaning age in rats affects maturational tempo and that the trait is transmitted trans-generationally (TG).
Hypotheses: TG effects of weaning involve epigenetic mechanisms and may be imprinted by one parent. We aimed to reveal phenotypic discordance upon paternal or maternal transmission and identify genes involved in this TG trait.
Methods: Rat pups were weaned by co-fostering on d16, d21 or d26. On d60 females and males mated within the weaning groups and we compared gene expression by Affymetrix exon microarrays (n=3-4) on d1 offspring livers of early- or late-weaned parents. In parallel, we evaluated phenotypic discordance upon paternal or maternal transmission.
Results: Growth was faster ($p< 0.01$) and BMI smaller ($p< 0.001$) in offspring of fathers (but not mothers) weaned on d16 vs. fathers weaned on d26; gonadarache ($p< 0.001$), vaginal opening ($p< 0.01$) and estrous of offspring ($p< 0.01$) were earlier upon paternal but not maternal transmission. A total of 89 probe sets were differentially expressed ($P< 0.005$) between groups. Analysis for enriched Gene Ontology indicated divergence ($P< 0.001$) in ROR-, PPARα-, PXR- and GR-activated pathways. Notably, mRNA levels for two genes were clearly higher ($P< 0.005$) in offspring of late-weaned slow-maturing parents, as confirmed by RT-PCR: MFSD2A and P450-oxidoreductase (POR).
Conclusions: Maturational tempo related to weaning age is TG-transmitted by fathers. MFSD2A and POR play crucial roles, the former in body growth and lipid metabolism, and the latter in regulation of retinoic acid levels during early embryonic development, previously shown to be transmitted by fathers. MFSD2A and POR are both regulated by PPARα whose enhancer is methylated in inverse correlation with its expression levels, indicating a possible epigenetic mechanism for the paternal TG inheritance of the weaning age-trait of maturational tempo.

FC5-145 Programming and Epigenetics

From bench to bedside: miR-155 and miR-370 are related with genotype and glucose tolerance state in cystic fibrosis (CF)

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Background: CF-Related-Diabetes has a variable presentation, possibly due to unknown epigenetic regulation of insulin sensitivity. We showed reduced FOXO1 content in CFcells. Non coding RNAs are important in epigenetic regulation.
Objective and method: We aimed to perform a transcriptional profiling of all known miRNAs in CFBE41o- (homozygous F508del), and in their normal counterparts(16HBE14o-), in IB3 (heterozygote compound F508del), and in C38 cells (IB3 rescued) using TaqMan human microRNA low density array (Applied Biosystems).
Results: We selected miRNAs up- and down-regulated differing by a Log_{10} $>\pm 1$ factor (N= 120) and analysed the validated targets (www.mirdb.org). We selected 2 miRNAs related with insulin sensitivity with a Ct in the range set for identification in human serum. Prior to this we tested whether miRNAs could be quantified by TaqmanMicroRNA assays from RNA samples purified from human serum; miR-16, and miR-93 were used as housekeeping miRNAs. CF affected(N= 25) and control subjects(N=20) were evaluated. dCts were normalized with respect to an appropriate pool of dCt controls, and expressed as fold change. First we studied normal physiology. MiR-155 was downregulated by $2Log_{10}$ in puberty in homozygotes (H) compared with the other stages. Based on genotype (H F508del, He F508del and other mutations with one in functional class 1 and 2), in H, miR-155 was up-regulated by Log_{10} with respect to the other genotypes ($p< 0.05$). miR-370 was upregulated by $1Log_2$ in H with respect to other genotypes. Both miR155 and miR370

had as predicted target the 3'UTR of the FOXO1 gene (RNA22-HSA https://cm.jefferson.edu/ma22v1.0-homosapiens; targetscan.org).
Based on glucose tolerance state, established using an OGTT, miR-155 was up-regulated ($3Log_{10}$, P:0.005) in serum of patients with reduced versus normal glucose tolerance.
Conclusions: In vivo data matched in vitro findings, confirming an effect of genotype and a relationship with glucose intolerance.

FC5-146 Programming and Epigenetics

Chromatin profiling of germ cell cancer cell lines reveals differences in active enhancer states between seminomas and non-seminomas: a GENVIRONMENTAL connection?

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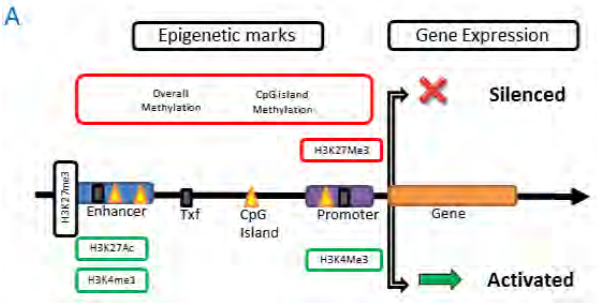
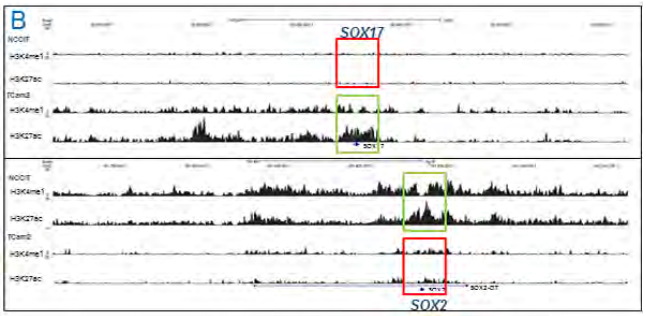
Background: Interplay between (epi)genetics and environment is involved in formation and maintenance of normal gonadal development. Primordial germ cells (PGCs) undergo epigenetic modifications. A disturbed micro-environment during this process might result in disturbed fertility and malignancy. Germ cell cancers (GCC) originate from PGCs/gonocytes, and are subdivided into seminomas (SE) and non-seminomas (NS). Investigation of histone modifications could be informative to elucidate the mechanisms involved in the formation of GCC, and might identify markers for risk stratification, diagnosis and prognosis.
Objective: Gain insight into the role of histone modifications in development of GCC.
Methods: We studied two well characterized GCC-cell lines, TCam-2 and NCCIT, representative for SE and NS respectively. Chromatin immunoprecipitation was performed, using antibodies against three histone modifications; H3K4me1, H3k4me3 and H3K27ac. Enriched DNA was sequenced on the SOLiD 5500xl sequencer.
Results: We identified a defined pattern of active regulatory regions within the genome. Initial analysis matched the classification of the cell lines; SOX17 was strongly enriched for H3K4me1 and H3K27ac in TCam-2 compared to NCCIT cells, whereas the opposite pattern was observed for SOX2. Detailed investigation in the cell lines and primary GCC samples, is ongoing.



[Schematic representation of epigenetic changes
A. Regulation of gene expression controlled by DNA methylation and histonmodifications. Histonmodifications occor at enhancer or promoter sites and can be either activating ot silencing.]



[Figure. Schematic representation of epigenetic changes
B. Display of H3K4me1 en H3K27ac tracks for both NCCIT and Tcam-2. The top and bottom boxes indicate a repressive state and the two middle boxes an active state.]

Conclusion: We generated epigenetic signatures of representative cell lines for SE and NS. Extensive analyses, and confirmation of primary patient samples, will give novel insights into the epigenetic differences and understanding of the patho-biology of GCC, possibly linking genetic and environmental risk factors.

FC5-147 Programming and Epigenetics

CDKN1C mutation in the PCNA domain is a new mechanism for Silver-Russell syndrome

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Background: Silver-Russell syndrome (SRS) is a rare fetal and post natal growth disorder, with loss of methylation (LOM) at the paternal ICR1-11p15 locus for about half of the patients. *CDKN1C* is an inhibitor of cell proliferation. This gene is included in the 11p15 region and is imprinted. About 5% of Beckwith Wiedemann syndrome (BWS, an overgrowth syndrome which represents a clinical and molecular mirror of SRS) is caused by loss of function mutations on the maternal allele of *CDKN1C*. Furthermore, mutations in the PCNA domain of CDKN1C have recently been implicated in the rare IMAGe syndrome (including intrauterine growth retardation (IUGR) and neonatal adrenal insufficiency).
Objective and hypotheses: As SRS and IMAGe syndrome share common clinical signs (especially IUGR), we investigated a cohort of clinically diagnosed SRS patients with no 11p15 ICR1-LOM for *CDKN1C* mutations.
Methods: The whole coding sequence and intron-exon boundaries of *CDKN1C* were analyzed in a cohort of SRS patients with no ICR1 LOM. Impact of *CDKN1C* variants on cell cycle was determined by flow cytometry.
Results: We identified a new mutation in the PCNA binding domain of CDKN1C in a familial case of SRS with four generations of severe IUGR and SRS phenotypic features (according to a validated clinical score) with no adrenal insufficiency. The mutation was identified in all of the 5 tested patients, and absent from one patient with a normal phenotype. Each patient inherited the mutation from her mother, in accordance with the imprinted character of CDKN1C. Functional studies showed no impact of this mutation on cell cycle (as it has been described in IMAGe mutations), suggesting an effect independent from the cyclin dependant kinase inhibitor domain.
Conclusions: *CDKN1C* mutations represent a new cause of SRS, completing the molecular mirror between SRS and BWS. Investigation of *CDKN1C* should be discussed for familial cases of SRS with no 11p15 ICR1-LOM.

FC5-148 Programming and Epigenetics

Higher blood pressure in 5- to 7-year-old children born preterm as compared to children born at term is not related to cortisol excretion rate

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Background: Data on blood pressure (BP) in prepubertal children born preterm as compared to peers born at term are scarce. Differences in BP might be related to differences in cortisol metabolism.
Objective and hypotheses: To compare BP and cortisol metabolism between 5- to 7-year-old children born preterm and born at term. We hypothesized children born preterm to have higher BP values and higher overall urinary cortisol excretion than their peers born at term.
Methods: BP was measured in 236 children (preterms n=116; gestational age 29.8 ± 2.6 (30; 24-33) weeks [mean ± SD (median; range)]) using an automatic oscillometric device. Urinary steroid profiles were determined in 24-hour urine samples using gas chromatographic-mass spectrometric analysis. To assess overall daily cortisol excretion, the seven major urinary glucocorticoid metabolites THF,α-THF,α-cortol,β-cortol, THE, α-cortolone, and β-cortolone were summed. The values were adjusted to creatinine excretion and to body surface area.
Results: Length-adapted systolic BP and diastolic BP were higher in preterms than in children born at term ($p < 0.0001$ and $p < 0.0003$, respectively). Multiple regression analyses including further variables with potential influence on BP confirmed the independent association between prematurity and SBP (p=0.0022) and DBP (p=0.0077).
Overall daily cortisol excretion was lower in preterms than in terms (p=0.0113). Multiple regression analyses including further variables with potential influence on cortisol excretion rate confirmed an independent association between prematurity and lower daily cortisol excretion (p=0.0043).
Conclusions: This study indicates BP to be higher after preterm birth as early as from the age of 5 to 7 years onwards, which might have implications for cardiovascular health later in life. Differences in excretion rates of cortisol metabolites do not offer an explanation for elevated BP in preterms.

FC5-149 Programming and Epigenetics

Clustering of cardio-metabolic risk factors during childhood and adolescence in subjects born small and large for gestational age

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Background: Subjects born small (SGA) and large (LGA) for gestational age have an increased risk of cardio-metabolic diseases already during the prepubertal age. Nevertheless, the progression of their cardio-metabolic profile from childhood to adolescence has not been fully explored.
Objective and hypotheses: To assess potential changes in the cardio-metabolic profile from childhood to adolescence in SGA and LGA children compared to those born appropriate (AGA) for gestational age.
Methods: Seventy-eight subjects (27 AGA, 26 SGA, 25 LGA) were recruited and evaluated during childhood (mean age 8.2±1.7 yr) and adolescence (mean age 13.2±1.9 yr). Adiposity (BMI), blood pressure (BP), insulin resistance (IR) (HOMA-IR), lipid profile and asymmetric dimethylarginine (ADMA) were assessed.
A cardio-metabolic risk score was also applied, and this consisted in assigning a value of 1 in the presence of obesity, abnormal BP, IR, dyslipidemia and high ADMA, or a value of 0 in their absence, and in calculating the sum of points assigned to each parameter.
Results: HOMA-IR and ADMA were higher in SGA and LGA than AGA subjects both during childhood and adolescence. The cardio-metabolic score was higher in SGA and LGA than AGA children, and these differences increased during adolescence.

	CHILDHOOD				ADOLESCENCE			
	AGA	SGA	LGA	P	AGA	SGA	LGA	P
HOMA-IR	1.5 ±0.5	2.5±1.2	2.2 ±1.3	0.01	2.6 ±1.1	4.1±1.6	3.8 ±1.3	<0.001
ADMA	0.4 ±0.2	0.9±0.6	0.8 ±0.7	<0.001	0.3 ±0.2	0.7±0.2	0.7 ±0.4	<0.001
Cardio-metabolic score	1.1 ±1.0	1.8±1.1	1.9 ±1.1	0.01	1.2 ±1.2	2.1±1.4	2.2 ±1.1	0.01

[Cardio-metabolic markers of the study population]

Interestingly, during childhood and adolescence SGA and LGA showed a higher prevalence of IR (P=0.04 and P=0.008, respectively) and high ADMA (P=0.02 and P=0.009, respectively) than AGA subjects.
Conclusions: SGA and LGA showed an adverse cardio-metabolic profile during childhood than AGA children, with a worsening of this profile during adolescence. These findings suggest a worrying overtime tracking of cardio-metabolic risk in SGA and LGA populations.

FC6-150 Glucose Metabolism

IGFBP-2 enhances insulin signalling and glucose uptake in human skeletal myotubes

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Background: Insulin-like growth factor binding protein-2 (IGFBP-2) levels are reduced in obesity and type 2 diabetes mellitus, and IGFBP-2 over-expression protects against these conditions. Mechanisms are unclear.
Objective and hypotheses: To examine the effect of IGFBP-2 on phosphatidylinositol 3-kinase (PI3K)/AKT signalling and glucose uptake in skeletal muscle. Our hypothesis was that IGFBP-2 would directly improve insulin signalling and glucose uptake.
Methods: All experiments utilised *in-vitro* cultures of fully-differentiated human skeletal myotubes (HSM), held in serum-free media and in the absence of exogenous IGF-1. Treatments were as follows:
A) IGFBP-2 (0 or 100ng/ml for 24h) prior to insulin stimulation (0 or 100nM insulin for 30mins);
B) IGFBP-2 or insulin stimulation in the absence/presence of Wortmannin (PI3K inhibitor; 100nM);
C) Human-specific IGFBP-2 small-interfering RNA (or scrambled siRNA as control) for 24h prior to insulin-stimulation;
D) Silencing of IGFBP-2 (as in C), prior to dosing with 'add-back' IGFBP-2 for 24h and then insulin stimulation. Outcomes included phosphorylation of $AKT^{(ser473)}$ (pAKT) in cell lysates by Western immunoblotting and glucose uptake using 2-deoxyglucose uptake assays, was also quantified in C.
Results:
A) Basal pAKT was increased fivefold in the presence of IGFBP-2 ($p< 0.05$), while insulin-stimulated increases in pAKT were doubled when IGFBP-2 was present ($p< 0.05$).
B) Wortmannin completely ablated insulin-induced ($p< 0.001$), and IGFBP-2-induced ($p< 0.01$) increases in pAKT.
C) IGFBP-2 gene silencing reduced insulin-stimulated pAKT by 61% ($p< 0.001$) and glucose uptake by 22% ($p< 0.05$).
D) Adding back IGFBP-2 (100ng/ml) completely restored and further enhanced insulin signalling (400%; $p< 0.05$).
Conclusions: These findings indicate that IGFBP-2 directly enhances PI3K/AKT signalling and glucose uptake in HSM.

FC6-151 Glucose Metabolism

GLP1 levels and HMW adiponectin in children born small for gestational age with catch-up vs children born small for gestational age without catch-up; a possible explanation for their differences in carbohydrate metabolism and food intake

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Background: The majority of the population born small for gestational age (SGA) shortly reaches normal anthropometric values but then develop insulin resistance.This population is also characterized by their high food intake, many being voracious.In contrast, a smaller amount of patients SGA never reach normal anthropometric values but have a normal carbohydrate metabolism and a low food intake many developing innapetence. Until now no explanation have been established for this phenomenon: a common antecedent, SGA, with two very different phenotypes.
GLP1 regulates gastric emptyng and improves carbohydrate metabolism.
Objective and hypotheses: Compare the levels of GLP-1 and HMW adiponectin in children SGA with catch-up and children SGA without catch-up. Children SGA with catch-up will have a flat GLP1 curve with lower levels of HMW adiponectin while children SGA without catch up will develop a curve with a pronounced peak with higher levels of HMW adipoctenin.
Methods: Case control study comparing 10 patients SGA with catch-up and 10 patients SGA without catch-up from a general pediatric clinic. GLP1 and glycemia were measured at 0-30-60-90 and 120 minutes in glucose load test. A single sample of HMW adiponectin was measured. Qualification of appetite was realized by the parents of the patient.
Results: Significant differences were found between the curves of GLP1 and Glycemia of children SGA with catch-up vs children SGA without catch-up. GLP1 curves differ p= 0.012 (Huynh-Feldt epsilon method) Glycemia curves differ p= 0.043 (Huynh-Feldt epsilon method) Spearman correlation of 53.2% between GLP1 at 30 minutes and HMW adiponectin in children SGA without catch-up. Appetite difference between the two groups in linkert scale had P< 0.001.
Conclusions: GLP1 curve in children SGA with catch-up is flat while the GLP1 curve of children SGA without catch-up has a pronounced peak. This result is a good explanation for their different carbohydrate metabolism and food intake.

FC6-152 Glucose Metabolism

Higher relative risk for multiple sclerosis in a paediatric diabetes population: analysis from DPV database

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Background: Diabetes mellitus type 1 (T1D) and multiple sclerosis (MS) are typical autoimmune diseases in children and young adults. Although the pathomechanism is rather unclear, T1D and MS show individual co-occurrence.
Objective and hypotheses: To asses the co-occurrence of T1D and MS by estimating the relative risk for MS in a pediatric diabetes population and to define possible influencing factors.
Methods: Within the DPV-Wiss-project, from January 1995 to October 2012, data of 56,653 patients with T1D (younger than 20 years) were collected in 248 centers in Germany and Austria. Population based German and Mid-European disease registers for MS were used to compare prevalence data. Multivariable regression analysis was used to identify confounders for co-occurrence of T1D and MS.
Results: Hazard ratio for MS in T1D was estimated at 3.35 to 4.79 (95% CI: 1.56 to 7.21 and 2.01 to 11.39, respectively). As influencing factors on MS incidence within the DPV database could be identified immigration status in all (p< 0.05) and thyroid antibodies in males only (p= 0.05). The month of birth pattern was higher during the spring and summer months in the T1D & MS in comparison to the T1D population.
Conclusions: The present cohort study demonstrates a higher risk of co-occurrence of MS in a pediatric diabetes population. Immigration status and thyroid antibodies in males were independent risk indicators for incidental rate of MS. Diabetic parients born during spring and summer had a higher risk to develop MS. We suggest that environmental factors modulate the individual's risk for the co-occurrence of both diseases.

FC6-153 Glucose Metabolism

Linear association between household income and metabolic control in children with insulin-dependent diabetes mellitus in spite of free access to health care

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Background: In health care systems with a user fee, the impact of socio-economic factors on pediatric IDDM control could be due to the cost of accessing care.
Objective and hypotheses: Whether household income shows a linear association with the average glycosylated hemoglobin (HbA1c) of children and adolescents with IDDM in a jurisdiction with free universal access to health care has never been evaluated.
Methods: We used a linear regression to examine the association between normalized average HbA1c of 1,766 diabetic children (diagnosed at our institution from 1980 to 2011 before 17 years of age) and the median household income of their neighborhoods (obtained from Statistics Canada, 2006 Census data).
Results: We found a negative linear association (p< 0.001; r=-0.2) between level of income and metabolic control assessed by HbA1c after controlling for sex, age at diagnosis, duration of diabetes, ethnicity, geographical factors and change of measurement methods of HbA1c across time. For every increase of 15,000$ in annual income, HbA1c decreased by 0.1%.
Conclusions: We report a linear association of household income with metabolic control of IDDM in childhood. Given that Canada has a system of free universal access to health care, confounding by access to care is unlikely. Considering the impact of poorly controlled IDDM in childhood on the development of long-term complications, our findings suggest that the higher complications rate found in adults of low socio-economic status might originate from the poor control that they experienced in their childhood.
Support for the care of IDDM children from low-income neighborhoods should be increased.

FC6-154 Glucose Metabolism

Early onset diabetes and hypoglycaemic seizures are associated with deteriorating IQ: evidence from a cohort with type 1 diabetes mellitus followed-up for 12 years from diagnosis

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Background: Intelligence quotient (IQ) is lower in young people with type 1 diabetes (T1DM) relative to healthy controls (HC). Impairment may be related to disease variables such as metabolic control history. No study has yet investigated longitudinal change in IQ from diagnosis in childhood to neurodevelopmental maturity in young adulthood.
Objective: To investigate within-subject change in IQ over the first 12 years of type I diabetes compared with HC, and the relationship to illness-related variables.
Method: Participants with type 1 diabetes recruited at diagnosis (N=106, age 1-14 years at study onset, mean age at follow-up 20.5yrs ±4.3) from The Royal Children's Hospital and followed up over 12 years. Age of illness onset, metabolic control and seizures were recorded prospectively. HCs (N=75) were also followed longitudinally (N=75, mean age at study entry 1-14 years, mean age at follow up 21.0yrs ± 3.8yrs). Within-subject change in IQ was investigated between diabetes onset and 12 years post-diagnosis. The grouping variables used were
a) T1DM vs. HC;
b) early onset diabetes (≤5 years) vs. later onset diabetes;
c) history of hypoglycaemia-related seizure /s vs. no history of seizure/s and
d) poor metabolic control (HbA1c >9% for more than 33% of lifetime measurements) vs. good metabolic control.
Results: Change in IQ did not differ between T1DM and HCs, or between T1DM participants with good vs. poor metabolic control. Those with early onset illness showed a greater decrement in Performance ($p < .001$) and Full-Scale IQ ($p < .001$) between diagnosis-12 years than later onset participants. Participants with a history of seizures showed a larger decrement in Verbal IQ ($p=.004$) from 1-12 years than those without seizures.
Conclusions: These novel longitudinal findings confirm previous cross-sectional findings that early disease onset is associated with a deterioration of Performance IQ over time and that hypoglycaemic seizures affect Verbal IQ.

FC6-155 Glucose Metabolism

Neonatal diabetes mellitus in a prospective cohort of 174 patients: frequent association with developmental defects and neuropsychological dysfunction

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Background: Neonatal diabetes mellitus (NDM) is a rare **genetic** form of pancreatic beta-cell dysfunction leading to hyperglycaemia early in life.
Aim: To compare phenotypic features and clinical outcome according to the genetic subtypes in a cohort of patients with NDM diagnosed before the age of one year, without beta-cell autoimmunity and with normal pancreas morphology.
Methods: We prospectively investigated patients from 20 countries referred to the French NDM Study Group from 1995 to 2010, for associated genetic abnormalities: alterations in the 6q24 locus and in the genes encoding the K_{ATP} channel *(ABCC8* and *KCNJ11)* and preproinsulin (*INS)*.
Results: We identified genetic causes in 128 out of 174 (74%) probands that consisted in 6q24 abnormalities (n=40), mutation in *KCNJ11* (n=43), *ABCC8* (n=31) or *INS* (n=14). We reported developmental delay associated or not with epilepsy (DEND and iDEND syndrome) in 24% of probands with K_{ATP} channel mutations. We also evidenced Developmental Coordination Disorder (particularly visual-spatial dyspraxia) or attention deficits in all of the 27 probands (aged 5 months to 19 years) who had refined neuropsychological and psychomotor investigations in the same center and tested normal in a standard neurological examination. We reported specific features of 6q24 genetic subtype as compared to K_{ATP} subtype: developmental defects involving the heart, kidneys or urinary tract (22% vs 3%, p=0·002), intra uterine growth retardation (92% vs 48%, $p < 0{\cdot}001$), and early age at diagnosis (median 5 days [1-120] vs 45·5 days [1-278], $p < 0{\cdot}001$). Remission of NDM occurred in 89 (51%) probands (median follow up 4·1 years [49 days-34·3 years]). Recurrence probability was high, without difference between the 6q24 and

the K_{ATP} channel probands (82% vs 86%, p=0·36, respectively).
Conclusions: NDM is frequently associated with neuropsychological or developmental defects specific to a genetic subtype and deserves specific multidisciplinary assessment.

FC7-156 GH and IGF in Health and Disease

GH signalling independent of IGF-1 induces increased linear bone growth in SOCS2 knockout mice

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Background: Growth hormone (GH) signalling is essential for post-natal linear bone growth. The systemic/local mechanisms responsible for GH action remain unclear as the importance of liver derived IGF-I on linear growth has been challenged.
Objective and hypotheses: To unravel the mechanisms of linear bone growth we exploited the Suppressor of Cytokine Signalling (SOCS2)-2 KO mice which have enhanced growth despite normal systemic IGF-1 and GH levels.
Methods: Growth plates were micro-dissected from WT and SOCS2 KO bones and IGF-1 transcript levels assessed. Embryonic day 17 metatarsals were cultured from WT and SOCS2 KO mice in the presence of GH to assess downstream signalling and gene expression.
Results: *In vivo* data revealed no increase in *Igf1* expression in growth cartilage of WT and SOCS2 KO mice. These data were extended by *ex-vivo* metatarsal experiments. In response to GH, WT bones expressed increased SOCS2 transcript levels. SOCS2 KO metatarsals showed increased STAT5 phosphorylation compared to similarly treated WT metatarsals. Increased STAT5 activation of SOCS2 KO metatarsals following GH challenge was associated with increased linear growth over a 12-day-period whereas the growth of GH treated WT bones remained unchanged. Transcript and cultured medium analysis carried out on days 7 and 12 revealed no change in IGF-1 levels despite increased growth in SOCS2 KO metatarsals. IGFBP3 levels showed a modest increase in response to GH in day 12 WT metatarsals. SOCS2 KO metatarsals showed greatly increased IGFBP3 levels in response to GH at all-time point studied. Moreover, GH remained stimulatory to SOCS2 bone growth in the presence of an IGF-1R inhibitor (NVP-AEW541).
Conclusions: These studies emphasise the importance of SOCS2 in the regulation of GH stimulation of linear bone growth and indicate that GH can enhance linear growth by initiating molecular pathways intrinsic to the growth plate that are independent of local IGF-I production.

FC7-157 GH and IGF in Health and Disease

Multiple perturbations to the Insulin-like growth factor 1 pathway and adult energy homeostasis following disruption of mouse chromosome 12 imprinting

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Background, objective and hypotheses: Disruption to insulin-like growth factor signaling pathways during early life causes growth retardation and defects of developing metabolic organs that can alter set points of energy homeostasis for a lifetime. Inheritance of two maternal copies of human chromosome 14q32.2 (Temple syndrome) causes severe fetal growth retardation and postnatal failure to thrive. Disruption of imprinted gene dosage in the syntenic region on mouse chromosome 12 also affects growth. Since it is not currently known if there is any involvement of the IGF axis in this phenotype we investigated if altering chromosome 12 imprinted gene dosage can affect IGF signaling.
Methods: We investigated mice with a transgene insertion at the imprinted domain of chromosome 12. This lesion causes misexpression of neighbouring genes such that expression of non-coding RNAs is elevated, and levels of Delta-like homologue 1 (Dlk1), Retrotransposon-like 1 (Rtl1) and Deiodinase 3 (Dio3) transcripts are reduced.
Results: We observed three key phenotypes in these mice;
1) embryonic growth retardation associated with altered expression of IGF1 binding proteins;
2) perinatal failure to thrive accompanied by hypothyroidism and low serum IGF1. Unexpectedly this phenotype was Growth Hormone independent.
3) Adult animals had reduced glucose tolerance as a result of endocrine pancreatic insufficiency.
Conclusions: We propose that all of these phenotypes are attributable to impaired IGF action, and show for the first time that the chromosome 12 cluster in the mouse is an imprinted locus that modulates the IGF signaling pathway. We propose that growth retardation observed in human Temple syndrome might have a similar cause.

FC7-158 GH and IGF in Health and Disease

Changes in serum insulin (Ins), insulin-like growth factor-I (IGF-I) and growth in GH deficient children treated with GH are associated with distinct gene expression networks

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Background: GH therapy increases Ins & IGF-I levels, alters Ins sensitivity & promotes growth. Genetic networks linking metabolic and growth responses are ill-defined.
Objective and hypotheses: Study associations between markers of Ins sensitivity [change in fasting glucose (gluc), Ins & homeostatic model assessment of Ins resistance (HOMA-IR) over 1 month (M1)], change in IGF-I over M1 & height velocity over 1 year (HV1) in relation to baseline gene expression.
Methods: Pre-pubertal children with GH deficiency (GHD; n=125) were enrolled from PREDICT (NCT00256126) & its long-term follow-up (NCT00699855). Whole blood gene expression was determined pre-treatment; biological markers assessed over M1 on GH & HV1. Associations between biological markers were assessed by partial correlation, adjusted for age, gender, BMI, GH peak & correlated with basal gene expression using rank regression. Network models were constructed from correlated gene expression (generating 'interactome' models). Highly connected network regions & associated specific function (hypergeometric test) were identified.
Results: M1 changes in gluc, Ins & HOMA-IR were correlated (all $P< 0.001$). M1 change in IGF-I correlated with Ins and HOMA-IR ($P< 0.05$) but not gluc. HV1 only correlated with M1 change in IGF-I ($P< 0.009$). The top network associated with overlaps between Ins & gluc and Ins & IGF-I interactome models was linked with *Adipocyte Differentiation* ($P< 0.001$) most notably involving the MED19 gene, a transcription co-factor. Overlap between IGF-I & HV1 models was associated with *RNA Processing* ($P< 0.002$) & *Lipid Metabolism* ($P< 0.02$) involving most notably genes for RBM3, an RNA-binding protein, & SCD, a fatty acid biosynthesis enzyme.
Conclusions: Genetic networks underlying metabolic & growth responses to GH in GHD have been identified; fat metabolism features in both. This approach could identify candidate genetic markers for specific aspects of GH action.

FC7-159 GH and IGF in Health and Disease

Body composition changes in adolescents with childhood-onset GH deficiency during the transition phase in relation to the GH retest peak: sex matters

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Background: The decision to restart GH treatment in transition patients with childhood-onset GH deficiency (GHD) is usually based on history, pituitary gland morphology and endocrine tests, but rarely on body composition changes.
Objective: We wanted to characterize quantitatively the body composition changes occurring in adolescents with GHD during 6 months off GH. Endpoint was the sum of total gain in fat mass (+kg) and total loss of lean mass (+kg) called *Body Composition Change Score* (BCCS).
Hypothesis: A high BCCS indicates severe GHD.
Patients: 39 adolescents (11 females) with GHD were re-examined at 16.3±1.8 y of age (mean±SD). At diagnosis age had been 7.0±3.2 y, height -3.2±0.6 SDS and stimulated GH peak 4.8±2.0 ng/ml.
GH treatment was stopped after 9.3±2.8 y at a near-final height of -1.2±1.0 SDS, 0.7 SDS below the target. BMI was 20.6±2.1 kg/m2. Irradiated patients were excluded.
Methods: Body composition was measured by dual-energy x-ray absorptiometry (DXA; Lunar, DPXL/PED) at GH stop and 6 months later. Retesting was performed using GHRH-arginine stimulation after 3 months off GH. GH and IGF-I were measured by in-house RIAs (cut-offs; GH< 15 ng/ml, IGF-I< 156 ng/ml).
Results: Four patients (two females) had severe GHD. Seven patients failed the GH test, but had normal IGF-I levels. Two patients had a normal GH test, but low IGF-I levels.
The mean BCCS determined by DXA was 3.4±4.3kg after 6 months off GH. In males, BCCS correlated inversely with the GH peak level (R=0.65; p< 0.001). GH< 15 ng/ml was always associated with a BCCS>5 kg. Importantly, this correlation was absent in females (R=0.05; p=0.88).
Conclusions: Short term changes of body composition after GH stop are a good measure of the severity of GH deficiency in male adolescents, but not in females. This sex difference may reflect the importance of the metabolic interaction of GH with testosterone.

FC7-160 GH and IGF in Health and Disease

Genetic characterisation of short children with potential defects of GH action by single gene sequencing

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Background: GH resistance or primary IGF-1 deficiency (PIGFD) presents with growth failure, low serum IGF-1 and normal or elevated serum GH. PIGFD comprises a spectrum of phenotypic and biochemical abnormalities for which genetic GH-IGF-1 axis defects may be causative.
Objective: Genotyping of PIGFD patients referred for sequencing of candidate genes.
Methods: From 2008-2013, 60 patients (40M 20F), median age 6.9 yr (range 0.4-30.0) with short stature (mean height SDS -3.56; range -9.37 to -0.17) were referred for genotyping. Depending on the phenotype, coding exons/intron boundaries of *GHR*, the *GHR* pseudoexon, *STAT5B*, *IGFALS*, *IGF1* and *OBSL1* were amplified by PCR from genomic DNA and the products purified and sequenced on an automated DNA sequencer (ABI 3700).
Results: Median serum IGF-1 levels were 38.8 ng/ml (range 1.4-95.0; below the normal IGF-1 range for age), with 16 patient samples being below the lower limit of the assay. GH secretion (n=52) was normal or elevated: median peak GH 18.8 µg/L (range 6.0-119.0). Eight patients did not have GH provocation tests, basal GH being elevated (median 60.0 µg/L; range 12.3-398.0). Sixteen patients (27%) had mutations in GH-IGF-1 axis genes: homozygous *GHR* (n=13; 6 pseudoexon), homozygous *IGFALS* (n=2; one novel c.1291delT) and heterozygous *STAT5B* (n=1). Heights in these subjects were -6.88 to -2.90 SDS. Two homozygous mutations were identified in the *OBSL1* gene (height SDS -4.9 and -5.7). Two other patients had hypomethylation in imprinting control region 1 in 11p15 or maternal UPD7 consistent with Silver Russell syndrome (SRS) (height SDS -3.66 and -4.28).
Conclusions: Genotyping is advised in short children with PIGFD. In 27% of PIGFD patients, all with heights < -2.5 SDS, a genetic abnormality demonstrated a major contribution to the pathogenesis. Diagnoses with similar phenotypes included SRS and 3M syndrome. In 67% (n=40) of patients no diagnosis was defined justifying further genetic investigation.

FC7-161 GH and IGF in Health and Disease

Increased IGF-1R affinity of insulin glargine, but not its metabolites, is caused by a faster association rate and, less, by a slower dissociation rate

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Background: Long-acting basal insulin analogs are developed to sustain insulin delivery and improve metabolic control in treatment of diabetes. Insulin analogs with slower dissociation from the insulin receptor (IR) have increased mitogenic vs metabolic actions. Although glargine, but not its metabolites M1 and M2, have increased IGF-I receptor (IGF-1R) affinity, the kinetics of these interactions has not been reported.
Objective and hypotheses: To investigate the kinetics of the interactions between the IGF-1R and insulin glargine, its metabolites M1 and M2, other insulin analogs or human insulin.
Methods: Association and dissociation rate constants of interactions between insulin / insulin analogs diluted in albumin free buffer and the immobilized extracellular part of IGF-1R were obtained by Biacore's SPR technology.
Results: Human insulin had a 40-fold lower IGF-1R affinity than IGF-I itself. Glargine had 2.5-fold higher affinity than human insulin, whereas the glagine metabolites M1 and M2 had 0.5-fold the affinity of insulin. Detemir had half the affinity of insulin and insulin lispro and aspart had affinities similar to that of insulin. The differences in rate constants underlying the different affinities disclosed that for glargine, the association rate is more affected than the dissociation rate constant. Detemir differed from human insulin by a 3-fold higher dissociation rate.
Conclusions: The increased IGF-1R affinity of glargine results from faster association and to some extent slower dissociation, suggesting a benign metabolic to mitogenic ratio as previous demonstrated in human muscle cells. The metabolites M1 and M2 that dominates after sc injection of Glargine demonstrates lower IGF-1R affinity.
Detemir studied in the absence of added albumin displayed a 2-fold lower IGF-1R affinity due to faster dissociation. Higher molar concentrations of Determir is requires due to its earlier reported 5-fold lower IR affinity.

FC8-162 Disorders of Sex Differentiation

Endocrine disruption in the human fetal testis. The effects of exposure to acetominophen (paracetamol) on testosterone production and steroidogenesis

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Background: Disruption of the human fetal testis by endocrine disruptors has been postulated as a cause of testicular dysgenesis syndrome. In-utero exposure of rats to paracetamol has been reported to reduce fetal testis testosterone production. We have shown that xenografting of human fetal testis tissue represents a system for investigation of the effects of proposed endocrine disruptors in the human fetus.
Objective and hypotheses: To determine the effect of exposure to paracetamol on testosterone production in human fetal testis xenografts.
Methods: Testis tissue from human fetuses (14-20wks gestation, n=6) were

xenografted into castrate male nude mice. Host mice received hCG to mimic the in utero environment, in addition to oral administration of either acetaminophen (350mg/kg/day) or vehicle, for 1 week. Graft testosterone production was determined by host seminal vesicle (SV) weight. RT-PCR and immunohistochemical expression of steroidogenic enzymes (3B-HSD, CYP17A1 and CYP11A1) were assessed. In addition, Wistar rats were exposed in utero to paracetamol and intratesticular testosterone was measured.
Results: Host SV weights were significantly reduced by 30% in paracetamol exposed grafts compared with vehicle exposed controls (10.0 v 14.4mg, $p< 0.001$). We also confirmed that a similar reduction (32%) of testosterone occurs with in utero exposure of male rats to paracetamol compared with vehicle (249.9 v 368.1pg/mg testis, $p< 0.0001$). Steroidogenic enzyme expression was similar in vehicle and paracetamol-exposed human fetal testis xenografts. Studies investigating the effects of exposure to paracetamol at lower doses are in progress and will be presented.
Conclusions: These results indicate that testosterone production by the human fetal testis may be reduced by in-utero exposure to paracetamol. These results may have important health and regulatory implications for determining the risk of in-utero exposure of paracetamol in humans.

FC8-163 FC8 - Disorders of Sex Differentiation

Gonadal localization and tumor risk markers in disorder of sexual development DSD patients during prepuberty

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Background: It has been proposed (Cools et al, 2005 and Li et al, 2007) that the co- expression of OCT 3/4 and testis-specific protein Y-encoded (TSPY) in dysgenic gonads represent a useful tool to predict testicular germ cell tumor (TCGT) risk.
Objective and hypotheses: To analyze OCT3/4 and TSPY immunoexpression in gonadal tissue of prepubertal (PP) DSD patients, as a function of gonadal localization, clinical phenotype (External Masculinization Score [EMS]), etiological diagnosis and chronological age at gonadectomy.
Methods: Thirty seven gonads from 36 DSD PP patients (46,XY : without molecular diagnosis, n=11; complete or partial androgen Insensitivity syndrome, n=5; SF1 mutations, n= 4; WT1 mutation, n=2; 45,X0/46,XY mosaicism, n=6; and 46,XX SRY negative, n= 8, and 10 PP normal testes (GrC) obtained from necropsies) were studied. According to gonadal localization, samples were divided in 3 groups: GrA (intraabdominal), n=15, GrI (inguinal) n=15, GrS (scrotal or labioscrotal) n=7. Age of gonadectomy (median and range) was: GrA 1.0 year(y) (0.1-12.0), GrI 1.6 y (0.3-14.0), GE 2.3y (0.04-12.3) and GrC 0.16y (0.003-15).
Results: Co-expression of OCT 3/4-TSPY was significantly higher in GrA 54% vs GrI+GrS 13%, p=0.038, Fisher exact test. There was a tendency to higher OCT3/4 and TSPY co-expression in EMS $\geq$7, n=11 (43%) than in EMS $\leq$3, n=9 (25%). No significative difference was found in DSD PP patients as a function of diagnosis or age at gonadectomy. Histological studies showed that carcinoma-in-situ was highly correlated with the co-expression of OCT3/4 and TSPY. No expression of OCT 3/4-TSPY was found in GrC.
Conclusions: These results might suggest that in DSD patients, abdominal localization might have a higher risk to develop TGCT. The lack of association with etiological diagnosis or age of gonadectomy might suggest that the risk of TGCT might be related to a disorder in fetal gonad morphogenesis.

FC8-164 FC8 - Disorders of Sex Differentiation

A case of Leydig cell hypoplasia associated with two distinct homozygous mutations of the human luteinizing hormone/chorionic gonadotropin receptor that include a novel mutation with unusual functional properties

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Background: Leydig cell hypoplasia is a rare autosomal recessive disorder in 46,XY individuals with a predominantly female phenotype. Inactivating mutations of the human luteinizing hormone/ chorionic gonadotropin receptor (hLHR) gene (*LHCGR*) are the basis for approximately 50% of patients with Leydig cell hypoplasia.
Objective and hypotheses: Our goals were to determine the genetic cause of Leydig cell hypoplasia in a 46,XY patient with a severe disorder of sexual development and characterize the properties of hLHR mutants identified.
Methods: We sequenced the exons of the LHCGR gene. The functional properties of a novel mutant hLHR were studied using recombinant mutant or wild-type receptors expressed in heterologous cells.
Results: Two different homozygous mutations in the patient's LHCGR were identified, an inactivating mutation (p.Gln18_Leu19ins9) previously reported in patients with Leydig cell hypoplasia and a novel mutation encoding a mutant receptor (p.G71R) with unique properties. hLHR(G71R) was expressed on the cell surface at reduced levels due to a decrease in the steady state amount of immature receptor and not to a block in transit of immature to mature receptor. The hLHR(G71R) at the cell surface exhibited increased binding affinity for hCG and an increased efficacy of hCG-stimulated cAMP signaling. Overall, the integration of the decreased cell surface expression and enhanced intrinsic hormone responsiveness of G71R caused a mild attenuation in hormone dependent signaling.
Conclusions: This patient is the first for whom two homozygous mutations of the LHCGR have been described as contributing to Leydig cell hypoplasia, one of which, the p.G71R, has highly unusual functional properties.

FC8-165 Disorders of Sex Differentiation

APOD bioassay confirms CAIS in a 46,XY newborn with female external genitalia in the absence of a coding AR-gene mutation

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Background: Although androgen insensitivity syndrome (AIS) is typically associated with inactivating AR mutations, many patients with clinical AIS lack a detectable mutation. We have previously established a bioassay to determine AR transcriptional activity through analysis of the androgen regulated AR target gene apolipoprotein D (APOD) in cultured genital fibroblasts.
Objective: To characterize AR function in cultured genital fibroblasts of a 46,XY newborn with clinically diagnosed CAIS but no coding AR mutation compared to two male control fibroblasts strains.

Methods: Newborn with completely female external genitalia and inguinal hernia on the left containing a testis; no uterus; karyotype 46,XY; plasma testosterone 1065ng/dl at age 2 weeks (normal range 14-363ng/dl for 46,XY males); AMH >14ng/ml; sequence analysis of AR and SRD5A2 genes; analysis of AR expression on the transcriptional and translational level as well as detection of dihydrotestosterone (DHT) induced APOD transcription in cultured genital skin fibroblasts.
Results: No mutation in the coding region of the AR and SRD5A2 genes could be detected in the patient. However, a c-547C>T nucleotide exchange was present in the 5'UTR of AR. AR transcription in the patient's fibroblasts was detectable at a similar level as compared to male control cells. Western blot analysis using an antibody directed against the N-terminus of the AR showed a truncated AR protein of approximately 75 kDa. While the control fibroblasts showed APOD induction of 3-4 fold, there was no induction in the patient's cells.
Conclusions: The lack of DHT-induced APOD transcription confirms the clinical diagnosis of CAIS in the patient by demonstrating androgen resistance at the functional level. The role of the c-547C>T exchange is not clear. Further studies are ongoing to unravel the underlying molecular mechanism. Our exemplary case demonstrates that the APOD-bioassay is a valuable tool to diagnose AIS on functional grounds.

FC8-166 Disorders of Sex Differentiation

Temporal changes in sex assignment based on data gathered from the I-DSD Registry

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Background: It is unclear whether the proportion of children with DSD who are assigned a male sex or a female sex has changed over time.
Objective and hypotheses: The aim of the analysis was to determine whether the appearance of the external genitalia assessed by the initial external masculinisation score (EMS) influenced the choice of sex of rearing and whether this changed over time.
Methods: The analysis was performed on the data gathered in I-DSD Registry until February 2013. We defined the initial external masculinisation score as the EMS assessed in the neonatal/infancy period or in older cases as the EMS before any intervention. The cases were divided according to year of birth into three groups: those born before 1990, from 1990 till 1999 and born after 1999.
Results: In partial androgen insensitivity syndrome (total n=109) the number of cases of male sex assignment (total n=78) as well as the proportion of such cases (from 1,38 to 5,29) increased over time. There was a significant difference in the initial EMS between the group raised as boys (median 6, range 2-11.5) and the group raised as girls (median 2, range 0-8) p=0,000000. This significant difference of the initial EMS between the two sexes was observed over time. However, there was no significant difference in the initial EMS over time in the group raised as girls or in the group raised as boys. In fact, the degree of overlap for the initial EMS between the two sexes increased with time.
Conclusions: These data clearly show that there are clear trends in sex assignment and that they have been influenced by factors other than the appearance of the external genitalia. There is a need to explore the underlying reasons for these trends.

FC8-167 Disorders of Sex Differentiation

Phalloplasty: a valuable treatment for men with disorders of sex development and micropenis?

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Background: An abnormally short penis size persisting into adulthood may become a major cause of dissatisfaction and sexual dysfunction. Can phalloplasty, generally applied in the context of transgender surgery, be a valuable treatment for men with micropenis?
Objective: We aimed to assess psychosexual development and long-term (> 1 year post surgery) sexual Quality of Life (QoL) outcomes after phalloplasty in 46, XY male patients with penile insufficiency.
Methods: Ten men (aged 20 - 43 years) were retrospectively studied 14-92 months after phalloplasty (80% radial forearm free flap, 20% anterolateral thigh flap). All but one had erectile implant surgery 1 year after phallic reconstruction. Sexual development and Qol were assessed with a semi-structured interview and outcomes were compared to those of men with hypospadias repair and control men (Mureau et al., 1995).
Results: There were no significant differences in mean age at which sexual milestones were reached and all had had intercourse with orgasm and ejaculation after phalloplasty. However, even with sexual experience, 60% was inhibited in seeking sexual contacts, compared to 40% of hypospadiac patients ($p=0.25$) and 11% of controls ($p< 0.00$). Moreover, neophallus sensitivity was said to be less than previously hoped for and scars at the donor site were important. Five men developed urinary complications (stricture or fistula) and in one man the erectile implant had to be removed because of an aneurysmal swelling. Nevertheless, all indicated they would choose again for phalloplasty if necessary.
Conclusions: Phalloplasty opens new horizons for the treatment of 46, XY DSD patients with penile deficiency, but limitations of the technique should be emphasized prior to surgery. Psychological support should be an integral part of the management in alleviating the distress and impairment of sexual QoL. Publication of series with large numbers and longer follow-up is needed.

FC9-168 Adrenal Steroidogenesis

Identification and developmental changes in the expression of the enzymes from the "backdoor pathway" in prepubertal and pubertal human adrenal tissues

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Background: 17-Hydroxyprogesterone (17OHP) can be converted to dihydrotestosterone (DHT) via an alternative "backdoor" pathway that bypasses the conventional intermediates androstenedione and testosterone. In this pathway, 17OHP is converted to pdiol, which is an excellent substrate for the 17,20 lyase activity of CYP17A1 to produce androsterone. It appears that the backdoor pathway is a major route to DHT in pathological states in which 17OHP accumulates, including 21-hydroxylase deficiency and POR deficiency. However, the relevance of the backdoor pathway to human adrenal physiology is unknown.
Objective: Adrenal expression of AKR1C1-4, SRD5A1-2 and RoDH (HSD17B6) were studied using quantitative real-time RT-PCR.
Methods: According to a previous report (Baquedano et al, J Clin Endocrinol Metab 92:2215-22, 2007), human adrenal tissues (HAT) were collected from 3 postnatal age groups: Gr1: < 3 months, n=9, fetal zone (FeZ) involution; Gr2: 3 months to 6 yr, n=9, pre-adrenarche; and Gr3: >6 to 20 yr, n=8, post-adrenarche period.
Results: Gr3 mRNA levels (mean±SD, arbitrary units) of AKR1C1 (1.86±0.64) and AKR1C2 (1.89 ±0.50) were similar to GR2 but higher ($p< 0.05$) than in GR1 (1.14±0.39 and 1.13±0.32, respectively). AKR1C3 mRNA in Gr3 (3.06±0.78) was higher than in Gr1 (2.00±0.67) and Gr2 (1.24±0.54), $p< 0.05$. SRDA1 and RoDH cDNAs could be readily amplified from HAT without differences among age groups. SRDA2 and AKR1C4 mRNA levels were undetectable in the three age groups.
Conclusions: These results indicate that the postnatal human adrenal gland would express the enzymes to complete all the steps in the backdoor pathway to DHT. Taken together, these data support a physiological role of the back-door pathway as a mechanism of androgen production in the human adrenal gland. It could be suggested that the back door pathway could have a role in zona fasciculata, but not related to the development of zona reticularis at adrenarche.

FC9-169 Adrenal Steroidogenesis

New insights into the *in vivo* regulation of steroidogenesis: P450 side-chain cleavage enzyme (Cyp11a2) and ferredoxin (Fdx1b) specifically regulate interrenal steroid synthesis in zebrafish

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Background: Zebrafish is a well-established model in translational research. Recently, we have shown that the zebrafish cytochrome P450 side-chain cleavage enzyme, Cyp11a2, is the functional ortholog of human CYP11A1. CYP11A1 catalytic activity relies on electron transfer from ferredoxin (FDX1). *In vitro* data suggest modulation of CYP enzyme activity by redox cofactors. However, the physiological role of such mechanism *in vivo* remains unknown. In contrast to humans, zebrafish have two *fdx* genes, *fdx1* and *fdx1b*.
Objective: To define the role of the zebrafish *fdx* genes in steroidogenesis and to study regulatory mechanisms modulating steroidogenesis *in vivo*.
Methods: Gene expression was characterised by RT-PCR in embryos and adult tissues. Knockdown studies were performed using antisense morpholinos. Cortisol concentrations in zebrafish morphants were measured by liquid chromatography/tandem mass spectrometry.
Results: *fdx1* is expressed throughout development, whilst *fdx1b* and *cyp11a2* are expressed from 24 and 32 hours post-fertilisation, after the interrenal (counterpart of mammalian adrenal) develops. *fdx1* is ubiquitously expressed in adult zebrafish, whereas *fdx1b* and *cyp11a2* expression is restricted to steroidogenic tissues: interrenal, gonads and brain. Fdx1 knockdown results in early morphological defects during embryogenesis. Similarly to Cyp11a2, Fdx1b deficient larvae had impaired *de novo* steroidogenesis and developed late-onset metabolic abnormalities consistent with glucocorticoid deficiency. Interrenal insufficiency in Fdx1b morphants suggests a key role of Fdx1b in the regulation of interrenal steroidogenesis, which cannot be compensated by Fdx1.
Conclusions: Our data prove that Cyp11a2 and its redox partner Fdx1b are key regulators of zebrafish interrenal steroidogenesis. This study provides novel insights into the mitochondrial redox regulation of steroidogenesis and establishes zebrafish as a translational model to study adrenal physiology and disease.

FC9-170 Adrenal Steroidogenesis

Compensated mild androgen deficiency in boys with steroid sulfatase deficiency: evidence from steroid metabolomics

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Background: Steroid Sulfatase (STS) cleaves the sulfate moiety off steroid sulfates, including DHEAS, the inactive sulfate ester of the adrenal androgen precursor DHEA. Deficient DHEA sulfation, the opposite enzymatic reaction to STS, results in androgen excess by increased conversion of DHEA to active androgens. STS deficiency (STSD) due to deletions or inactivating mutations in the X-linked *STS* gene manifests with ichthyosis, but androgen homeostasis in STSD has not been studied in detail yet.
Objective and hypotheses: To investigate androgen synthesis and metabolism in STSD to explore whether circulating androgens are reduced in this condition.
Methods: Clinical assessment, serum and 24-h urine steroid analysis by mass spectrometry in 30 male patients with genetically confirmed STSD (age 6-30 years) and 45 age- and sex-matched healthy controls. Genetic analysis was performed by MLPA and Sanger sequencing.
Results: There were no apparent abnormalities in the physical development in STSD. Urinary steroid metabolome analysis revealed a decreased ratio of active androgen metabolites (Androsterone+Etiocholanolone) over androgen precursor metabolites
(DHEA+16hydroxy-DHEA+pregnenediol+5-pregnenetriol) as compared to controls ($p < 0.001$). 5α-reductase activity was increased in STSD ($p < 0.001$). Serum DHEA was decreased in all STSD age-groups ($p < 0.001$) but testosterone was only lower in the adult subgroup ($p=0.009$). Serum DHEAS did not differ significantly, but the ratio of DHEA/DHEAS was lower in STSD ($p < 0.001$).
Conclusions: Although pubertal development does not appear impaired in STSD, the steroid metabolome indicates mild androgen deficiency with elevated androgen precursor generation and increased 5α-reductase activity. We interpret the two latter findings as mechanisms of compensation, increasing substrate flow and peripheral androgen activation. Our findings provide the first *in vivo* evidence for a contribution of STS to androgen synthesis and metabolism.

FC9-171 Adrenal Steroidogenesis

Classic and non-classic 21-hydroxylase deficiency can be discriminated from P450 oxidoreductase deficiency in Japanese infants by urinary steroid metabolites

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Background: We previously reported 2-step biochemical diagnosis to discriminate classic 21-hydroxylase deficiency (C21OHD) from P450 oxidoreductase deficiency (PORD) by urinary steroid metabolites, pregnanetriolone / tetrahydrocortisone ratio (Ptl/THEs) for the first step and 11β-hydroxyandrosterone (11HA) for the second one (Koyama et al, Clin Chem 2012). The study group, however, did not include non-classic 21OHD (NC21OHD).
Objective: The objective of this study was to investigate whether C21OHD and NC21OHD (C+NC21OHD) could be biochemically differentiated from PORD.
Methods: We recruited 55 infants with C21OHD, 9 with NC21OHD, 18 with PORD, 67 with transient hyper 17α-hydroxyprogesteronemia (TH17OHP), and 1341 controls. All infants were Japanese with ages between 0-180 days. In addition to Ptl, THEs, and 11HA, we measured urinary pregnenediol (PD5) which was theoretically high in PORD because of 17,20-lyase impairment.
Results: The first step: C21OHD, NC21OHD, and PORD showed clear overlap with TH17OHP and control by Ptl/THEs using reported cutoff 0.02 (0.010-26 vs. < 0.001-0.028). In contrast, by Ptl using the age specific cutoffs 0.06 mg/g creatinine (0-10 days of age) and 0.3 mg/g creatinine
(11-180 days of age), we were able to differentiate these two groups
(0-10 days of age: 0.065-31 vs. < 0.001-0.052, 11-180 days of age: 0.40-42 vs. < 0.001-0.26) with 100% sensitivity and specificity. The second step: C+NC21OHD showed clear overlap with PORD by 11HA using reported cutoff 0.35 mg/g creatinine (0.13-22 vs. 0.07-0.22). On the other hands, by 11HA/PD5 with the cutoff 1.0, we were able to discriminate between C+NC21OHD and PORD (1.8-160 vs. 0.005-0.32) with 100% sensitivity and specificity.
Conclusions: Using Ptl and 11HA/PD5 could differentiate C+NC21OHD from PORD.

FC9-172 Adrenal Steroidogenesis

The effect of a novel compound heterozygous PAPSS2 mutation in two brothers with spondyloepimetaphyseal dysplasia on DHEA sulfation and androgen synthesis and metabolism

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Background: Mutations in the sulfate donor enzyme PAPSS2 cause spondyloepimetaphyseal dysplasia due to impaired proteoglycan sulfation and androgen excess by disrupting sulfation of the androgen precursor DHEA.
Objective: Here we report detailed *in vitro and in vivo* assessment of DHEA sulfation and androgen homeostasis in two brothers harbouring two novel PAPSS2 mutations.

Methods: Mutations were identified by whole exome sequencing and confirmed by bidirectional Sanger sequencing. DHEA sulfation was assessed in vitro in HEK293 cells co-transfected with WT/mutant PAPSS2 and WT DHEA sulfotransferase. Patients and parents underwent a DHEA challenge test (100mg) for in vivo assessment of DHEA sulfation and androgen synthesis; steroids were measured by mass spectrometry.
Results: Both brothers presented with skeletal dysplasia and short stature (height SDS -5.0/-4.1). The parents were of normal height; the mother had irregular periods and had required clomiphene for ovulation induction. Whole exome sequencing identified a compound heterozygous PAPSS2 mutation (p.G270D/p.W457GfsX2) in both patients. G270D showed 10% of WT activity while p.W475GfsX2 completely disrupted DHEA sulfation in vitro. Both brothers had significantly increased baseline androgen excretion and increased 5α-reductase activity also found in the mother who carried the inactivating frameshift mutation. After oral DHEA urinary androgen excretion increased twofold higher in the patients than in parents and controls. The father showed a normal increase in serum DHEAS after oral DHEA, which was reduced in the mother and absent in the brothers. Conversely, both patients showed significantly higher increases in serum DHEA, androstenedione and 5α-dihydrotestosterone after oral DHEA.
Conclusions: We undertook the first in vivo assessment of individuals affected by PAPSS2 mutations, revealing significant androgen excess and activation in both patients but also in the heterozygous mother with chronic anovulation.

FC9-173 Adrenal Steroidogenesis

Androgen receptor CAG repeat length in relation to phenotype of females with non-classical 21-hydroxylase deficiency

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Background: Non-classical 21-hydroxylase deficiency (NC21OHD) is a mild form of congenital adrenal hyperplasia associated with different degrees of postnatal virilization developing from infancy to adulthood. NC21OHD arises from partial deficiencies of 21-hydroxylase activity. The variability of symptom severity, despite the similarity of *CYP21A2* mutations, suggests the influence of other modifiers. The length of CAG repeats of the androgen receptor (*AR*) gene was found to be inversely correlated to transactivation activity of the human AR and to affect phenotypic features of several medical conditions characterized by hyper/hypo androgenism.
Objective and hypotheses: To investigate the associations between the CAG repeats and the severity of the phenotypic features of females with NC21OHD.
Methods: Determination of the *CYP21* genotype, degree of virilization and length of CAG repeats in 119 females with NC21OHD. Since the two alleles of the AR gene located on the X chromosome are differentially expressed in females due to the X inactivation phenomenon, the X-weighted biallelic mean (X-WBM) was calculated based on CAG repeat length adjusted to percentage of X-inactivation.
Results: A longer (>25) X-WBM of the AR repeats positively correlated with older age at diagnosis (20.1 Vs. 15.2 yr, *p=0.03*), shorter height SDS at diagnosis (-0.12 Vs. 0.42 SDS, *p=0.03*), older age at adrenarche (9.7 Vs. 8.2 yr, *p=0.02*) and gonadarche (11.0 Vs. 10.0 yr, *p=0.008*), and lower severity score (10.9 Vs. 11.9, *p=0.03*).
Conclusions: The CAG repeat length of the AR gene correlates with several clinical characteristics of females with NC21OHD and can explain, at least in part, the diversity of their phenotype.

FC10-174 Pituitary and Neuroendocrinology

Novel syndrome of microcephaly, endocrine, visual and renal abnormalities caused by ARNT2 mutation

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Background: Mutations affected hypothalamic development in humans have been identified in genes that affect isolated domains of hypothalamic function leading to restricted phenotypes, such as obesity or hypogonadotrophic hypogonadism.
Objective and hypotheses: We describe a previously unreported syndrome characterized by secondary (postnatal) microcephaly with fronto-temporal lobe hypoplasia, multiple pituitary hormone deficiency (cortisol deficiency, central hypothyroidism, abnormal growth, central diabetes insipidus), seizures, severe visual impairment and abnormalities of the kidneys and urinary tract.
Methods: Homozygosity mapping and exome sequencing were used to identify the pathogenic mutation in a highly consanguineous family with six affected children.
Results: A single novel homozygous frameshift mutation in the basic helix-loop-helix transcription factor gene *ARNT2* (c.1373_1374dupTC) was identified segregating between affected individuals. This mutation results in absence of detectable levels of *ARNT2* transcript and protein from patient fibroblasts compared to controls, consistent with nonsense-mediated decay of the mutant transcript and loss of ARNT2 function. We also show expression of *ARNT2* within the central nervous system (CNS), including the hypothalamus and retina, as well as the renal tract during human embryonic development.
Conclusions: We describe a mutation in a transcription factor known to regulate the development of the paraventricular, supraoptic and anterior periventricular nuclei in mice. The progressive neurological abnormalities and congenital hypopituitarism present in affected individuals demonstrate for the first time the essential role of ARNT2 in the development of the hypothalamo-pituitary axis, post-natal brain growth, and visual and renal function in humans.

FC10-175 Pituitary and Neuroendocrinology

The repressor activity of the Wnt/β-Catenin effector *Tcf3/TCF7L1* is required for normal hypothalamic-pituitary development

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Background: Aberrant development of the pituitary gland can result in the clinical manifestation of hypopituitarism. The Wnt/β-catenin pathway has been shown to be involved in normal organogenesis, terminal differentiation and the aetiology of pituitary tumours. However, the specific developmental roles during hypothalamic-pituitary development of some of the Wnt/β-catenin effectors, such as *Tcf3*,remains elusive.
Objective and hypotheses: To determine the function of Wnt/β-catenin effector *Tcf3* during hypothalamic-pituitary development.
Methods: Study of a conditionally deleted *Tcf3* (*Tcf3$^{Fl/-}$;Hesx1$^{Cre/+}$*) and *Tcf3$^{\Delta N/\Delta N}$* lacking the β-catenin interacting domain.
Results: Analyses of *Tcf3$^{Fl/-}$;Hesx1$^{Cre/+}$* mutant embryos reveal a mild hyperplasia of the pituitary gland, sometimes with the mis-location of the pituitary in the pharyngeal cavity. We show that *Tcf3* has a dual function and it is required in both the ventral diencephalon (VD) and anterior pituitary gland (AP). In the VD, absence of *Tcf3* results in aberrant VD signaling with rostrally expanded *Fgf10* and *BMP4* expression domains, leading to a broader region of the oral ectoderm being specified into Rathke's pouch.To assess if TCF3 is required to mediate transcriptional activation or repression of Wnt/β-catenin pathway, we studied a second murine mutant (*Tcf3$^{\Delta N/\Delta N}$*) expressing a mutant TCF3 lacking the β-catenin interacting domain, and therefore acting as a constitutive repressor. Interestingly, *Tcf3$^{\Delta N/\Delta N}$* embryos exhibit normal development of both the prospective hypothalamus and the pituitary gland , indicating that TCF3-repressing activity is essential. We report the identification of a novel mutation in *hTCF3* that compromises TCF3-repressing activity in a patient with septo-optic dysplasia (SOD), suggesting a contributory role of *TCF3* in SOD.
Conclusions: Our research demonstrates a critical role for the Wnt/β-catenin effector *Tcf3* during early development of the pituitary-hypothalamic axis in mice and humans.

FC10-176 Pituitary and Neuroendocrinology

Five novel mutations of *IGSF1* in six Japanese patients with X-linked congenital central hypothyroidism

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Background and objective: Congenital central hypothyroidism (C-CH) is a rare disease known to be caused by mutations of the genes encoding *TSHB* or *TRHR*, although the cause of the disease in a number of patients has not yet been clarified. The aim of this study was to clarify the molecular basis and endocrinological findings of C-CH.
Methods: We investigated six Japanese boys from six unrelated families with C-CH diagnosed by findings based upon low levels of free T4 and/or T3 and low basal TSH levels. Endocrinological evaluation of the anterior pituitary hormones was also carried out in these patients. At first in order to clarify identify the molecular basis of C-CH, whole-exome sequencing from two patients was carried out. We subsequently analyzed *IGSF1* by PCR direct sequencing in total six Japanese boys with C-CH. Furthermore, the cell surface expression and protein maturation of each mutant IGSF1s were studied *in vitro*
Results: All patients had CH and four had definitive prolactin (PRL) deficiency. Three patients were detected by neonatal screening based on simultaneous determination of TSH and free T4. The other patients showed short stature, failure to thrive and severe constipation. Whole-exome sequencing identified two novel variants in *IGSF1*. PCR-direct sequencing confirmed these variants (p.R1189X and c.3251_3252insC). We further analyzed *IGSF1* from four patients with CH and identified three novel mutations (p.V1082E, p.Q645X and c.2335+1G>A). *In vitro* study demonstrated that cell surface expression of R1189X and Q665X was not detected and its level of V1082E was decreased compared with that of wild-type, indicative of loss of function.
Conclusions: Our findings demonstrate that mutations of *IGSF1* are the cause of C-CH, and patients with *IGSF1* mutation have TSH and PRL deficiency.

FC10-177 Pituitary and Neuroendocrinology

The IGSF1 deficiency syndrome: clinical and biochemical characteristics of male and female patients

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Background: Recently, a novel X-linked syndrome was discovered in 11 families with central hypothyroidism, testicular enlargement and loss-of-function of IGSF1 (Sun et al., Nature Genetics 2012). We report on additional clinical and biochemical features of male and female patients with the IGSF1 deficiency syndrome.
Methods: All patients examined in the university clinics of Leiden, Amsterdam, Cambridge and Milan were included in this case series (24 males, 18 females). Detailed clinical and biochemical data were collected with a joint protocol and analysed in a central laboratory.
Results: Males (age 0-87 yrs) showed TSH deficiency (n=24), low prolactin (n=16) and transient partial growth hormone deficiency (GHD, n=3). With age, IGF-I tended to increase relative to age-matched reference ranges, and in some patients increased IGF-I values (>2 SDS) were observed at middle-age. Bioactivity of circulating IGF-I was normal. Pubertal testosterone production was delayed, as was the subsequent growth spurt and pubic hair development. Conversely, testicular enlargement started at a normal age but attained macroorchid size in all evaluable cases in adulthood. In most patients serum inhibin B was in the upper half of the normal range, while most activin A and anti-müllerian hormone levels were in the lower half. DHEA-S and DHEA were in the lower half of the normal range, and androstenedione in the upper half. BMI and fat mass were increased in most cases, but the metabolic syndrome was present only in three severely obese adults. Female carriers (age 32-80 yrs) showed mild TSH deficiency (n=5), normal prolactin, mildly increased BMI and fat mass, and IGF-I values in the upper half of the normal range or above.
Conclusions: The X-linked IGSF1 deficiency syndrome is characterized in males by central hypothyroidism, low prolactin, transient partial growth hormone deficiency, delayed puberty, macroorchidism and obesity. Central hypothyroidism was present in 25% of female carriers.

FC10-178 Pituitary and Neuroendocrinology

Linkage analysis of autosomal dominant hypopituitarism and maternal gingival fibromatosis in a large Finnish pedigree

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Background: Pituitary hormone deficiency combined with gingival fibromatosis is a rare hereditary syndrome, and the genetic defect causing it is currently unknown.
Objective and hypotheses: To describe the phenotypic features in a large Finnish family with pituitary hormone deficiency and gingival fibromatosis and to identify the genomic region harboring the causative genetic defect.
Method: We performed whole genome single nucleotide polymorphism (SNP) genotyping of 16 family members and performed linkage analysis.
Results: We describe a large Finnish family with autosomal dominant pituitary hormone deficiency and maternally inherited gingival fibromatosis. The most common manifestation was short stature and growth hormone deficiency. Other manifestations included hypogonadotropic hypogonadism, central hypothyroidism, and adrenal insufficiency. Strong linkage (LOD score > 3) was found in the chromosome 11p15 imprinted region, previously associated with several human growth-related disorders such as Silver-Russell, Beckwith-Wiedemann, and IMAGe syndrome. We also describe another family, originally from Argentina, displaying similar modes of inheritance for growth hormone deficiency and gingival fibromatosis. Identification of the causative mutation underlying this syndrome is currently ongoing.
Conclusions: In conclusion, we describe autosomal dominant pituitary hormone deficiency and maternal gingival fibromatosis segregating in a large Finnish family, mapping to chromosome 11p15.

FC10-179 Pituitary and Neuroendocrinology

Ancestral origin of two most prevalent mutations in the *PROP1* gene causing combined pituitary hormone deficiency in selected European populations

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Background: The *PROP1* gene whose recessive mutations cause combined deficiency of pituitary hormones, harbours two frequent mutations: c.296delGA and c.150delA. These mutations are responsible for a proportion of cases worldwide, with especially notable clustering of cases in Central and Eastern Europe. This suggests that each of the mutations has spread from its respective common ancestor.
Objective: The aim of our collaborative research project was to investigate whether this mutation clustering reflected a presence of a common ancestor.
Methods: We investigated 115 patients, homozygotes or compound heterozygotes for the c.296delGA or c.150delA mutations, originating from 106 families in 11 European countries. We genotyped 22 single nucleotide polymorphism markers flanking the *PROP1* gene in the distance of 9.6Mb that are not in mutual linkage disequilibrium in the general European populations (Pearson's $r^2 \leq 0.1$ for all pairs from HapMap, further verified in 94 unrelated population controls) - consequently, a finding of a common haplotype would be indicative of ancestral origin of the mutation. Haplotypes were reconstructed by Phase and Haploview software, and the age of the mutations estimated using the DMLE+ program.
Results: The c.296delGA mutation was carried on a haplotype spanning up to 0.7Mb around the *PROP1* gene, which yielded strong evidence ($p \leq 3 \times 10^{-4}$) for a common origin of this mutation arising about 112 generations ago. A similar founder effect was documented also for the c.150delA mutation that was carried on a haplotype spanning about 0.9Mb ($p \leq 0.003$); the estimated mutation origin was 97 generations ago.
Conclusions: Our large international multicentric study documents the existence of two common ancestors carrying c.296delGA and c.150delA mutations in the *PROP1* gene. This contradicts the previous assumption of mutation hot-spots in the *PROP1* gene.
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FC11-180 Congenital Hyperinsulinism

Gene expression profiling reveals possible role of growth factors in beta-cell hyperplasia in congenital hyperinsulinism

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Background: Congenital hyperinsulinism (CHI) is a clinically heterogeneous condition. Mutations in ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, UCP2 and HNF1A are known to cause CHI. There are 2 histological subtypes of CHI: diffuse and focal. Apart from the functional channel defect, β-cell hyperplasia has been observed in patients with diffuse CHI.

Objective and hypotheses: To understand the gene expression pattern in pancreatic tissue of patients with diffuse CHI when compared to normal controls and to compare the expression pattern in patients with known genetic aetiology of CHI with that of patients without a genetic aetiology.
Methods: Fresh frozen pancreatic tissue samples were obtained from 6 children with diffuse CHI who underwent near total pancreatectomy. RNA was extracted by standard techniques (TRIzol® Reagent). RNA Integrity was assessed by Agilent-derived RNA Integrity Number (RIN) and the presence of intact 18s and 28s bands on the Agilent Bioanalyzer trace. Gene expression microarray (standard Affymetrix techniques) was undertaken on the 6 diffuse CHI (4 with ABBC8 mutation and 2 without any known mutation) and 2 normal RNA samples.
Results: We observed significant overexpression of growth factors and their regulatory proteins like IGF1, IGF2 and IGF2BP3 in diffuse CHI patients. Uncoupling proteins like UCP2 are up regulated in diffuse CHI patients. An anti-apoptotic factor OLFM4 is overexpressed in one of the diffuse CHI patients without any known mutation. Growth factor receptor-binding protein (Grb14) is significantly downregulated in the other diffuse patient without any known mutation possibly enhancing insulin-induced signaling.
Conclusions: The data, first of its kind in CHI, has suggested the potential role of growth factors and anti-apoptotic factors in the β-cell hyperplasia in diffuse CHI. Agents targeting IGF pathways can be a potential therapeutic option to ameliorate the β-cell proliferation in CHI.

FC11-181 Congenital Hyperinsulinism

Network analysis can be used to predict signalling pathways associated with the pathobiology of congenital hyperinsulinism (CHI)

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Background: CHI is a complex condition associated with inappropriate insulin release and profound hypoglycaemia. A number of genetics causes of CHI are known, but for the majority of patients, the underlying aetiology is unknown.
Objective: We hypothesised that computational biology can be used to identify pathway ontology in CHI and to further define the pathophysiology of this rare disease.
Methods: Using bioinformatics, we generated an interaction network seeded by the known CHI-causing genes (*GLUD, SLC16A1, HADH, UCP2, KCNJ11, ABCC8, HNF1A, GCK, HNF4A*). The inferred network was generated using the Biogrid 3.1.94 interactome database and Cytoscape 2.8.3 to identify the primary interactors of CHI genes from all known physical and genetic evidence. Modular components of the network were analysed using spectral partition clustering. Biological pathways were then identified in association with clusters using a hypergeometric test.
Results: We found that the diverse range of genes causing CHI formed a core network - the CHI Disease Network, composed of highly connected members. Each module within the network (including Cellular Signalling, Nuclear Signalling, Growth Factor Signalling, Development and Biological Function) had nodes which were represented in a number of canonical biological pathways and could be implicated in the pathogenesis of CHI. Using a hypergeometric test false discovery rate (FDR) ≤ 0.001 these included: Tropomyosin Receptor Kinase Signalling ($5x10^{-5}$); RAF/MAP Kinase Cascade (5.3×10^{-5}), Neurotrophin Signalling (5.9×10^{-5}); BARD1 Signalling Events (1.3×10^{-4}); Presenilin Signalling (9.0×10^{-3}) and Integration of Energy Metabolism ($1.0x10^{-3}$).
Conclusions: Our data indicate that CHI-causing genes can be used to seed the CHI Disease Network, and identify canonical pathways which may be linked to the pathobiology of the condition.

FC11-182 Congenital Hyperinsulinism

Islet somatostatin receptor expression is altered in children with congenital hyperinsulinism (CHI)

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Background: Somatostatin (SST) analogues are widely used as "off-label" medications for CHI but their actions are associated with complications, including a worsening of symptoms and tachyphylaxis. Islets cells are known to express all five SST receptor (SSTR) subtypes, but SSTR expression in CHI pancreatic islets is unknown.
Objectives: We hypothesised that alterations in the expression of SSTRs are associated with clinical phenotypes and the loss of responsiveness to SST treatment.
Methods: Our study included 9 children with CHI and two adult control donors. All patients had either focal (n=5/9) or diffuse (n=4/9) CHI, carried gene defects in *ABBC8* or *KCNJ11* and underwent pancreatectomy for uncontrolled insulin release. We used antibodies directed against SSTR1-5 to examine protein expression in insulin-secreting β-cells and glucagon secreting α-cells following surgery. Network analysis of gene array data (http://www.ncbi.nlm.nih.gov/geo/ #GSE32610) was performed using Ingenuity Pathway Analysis.
Results: In comparison to control islet cells, patients with diffuse CHI showed altered expression of SSTR2-5, with a pronounced reduction of SSTR2 expression in α- and β-cells. However, there was no consistent alteration in SSTR expression in focal lesions. Three diffuse CHI patients underwent second pancreatectomy for recurrent hypoglycaemia. In two patients who were not treated with Octreotide in the inter-operative periods, SSTR2 expression was restored. Network analysis of gene expression revealed that biological pathways (e.g. Cell Cycle $P < 0.003$; Apoptosis $P < 0.0009$) coupled to SSTR2 rather than other SSTRs were selectively modulated in CHI tissue.
Conclusions: Our data indicate that functional SSTRs are expressed in islet cells from CHI patients and that the SSTR expression profiles for diffuse- and focal CHI are different. SSTR2 may be a key component in the clinical responsiveness of patients to somatostatin analogues.

FC11-183 Congenital Hyperinsulinism

Understanding the molecular basis of congenital hyperinsulinism due to autosomal dominant *ABCC8* and *KCNJ11* mutations

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Background: Adenosine 5′-triphosphate-sensitive potassium (K_{ATP}) channels are involved in regulating the release of insulin. Dominant mutations in ABCC8/KCNJ11 causing medically unresponsive Congenital Hyperinsulinism (CHI) have been reported but the molecular mechanisms are not clear.
Aims: To understand the molecular basis of medically unresponsive CHI due to novel dominant ABCC8/KCNJ11 mutations.
Patients and methods: We studied 14 patients with diazoxide unresponsive CHI who required a near total pancreatectomy. DNA sequencing revealed dominant inactivating heterozygous missense mutations (10 ABCC8 and 1 KCNJ11). Site directed mutagenesis was used to create mutant DNA, which was transfected into HEK293 cells for functional studies using radioactive Rubidium ($^{86+}$Rb). Wild type (WT) and mutant channels were exposed to five drug conditions; control (DMSO), 100μM diazoxide, 100μM diazoxide

and 10μM glibenclamide, 2.5mM NaCN and 20mM 2-deoxy-D-glucose and 2.5mM NaCN, 20mM 2-deoxy-D-glucose and 10μM glibenclamide. Efflux of $^{86+}$Rb was measured in a liquid scintillation counter using Cherenkov radiation. Western blot analysis was done using primary sheep anti-SUR1 NBD2 polyclonal antibody raised to peptide sequence ETLLSQKDSVFASFVRADK(C).
Results: D1506E, M1514K, G1485E and I1425L are located in the nucleotide binding domain 2 (NBD2) on the SUR1 protein. The $^{86+}$Rb efflux assay showed that mutant channels are unresponsive to activation by diazoxide and metabolic inhibition. WT channels show 20% and 26% $^{86+}$Rb efflux respectively whereas the mutant channels only exhibit 4% channel activity. Western blot analysis revealed that D1506E, M1514K and G1485E mutations were expressed in the cell.
Conclusions: The mechanism underlying medically unresponsive CHI caused by dominant mutations appears to be due the K_{ATP} channels inability to respond to channel agonists such as diazoxide. Mutations in NBD2 are likely to abolish the channels sensitivity to MgADP.

FC11-184 Congenital Hyperinsulinism

A pilot trial of supplemental omega-3-polyunsaturated fatty acids may reduce risk of hypoglycaemia in children with congenital hyperinsulinism (CHI)

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Background: The treatment for CHI, a severe condition of hypoglycaemia, is limited to oral diazoxide and octreotide injections. There is a need to improve therapeutic options in CHI. Omega-3-polyunsaturated fatty acids (PUFA) prevent arrhythmias by stabilising cardiac ion channels; similarly MAXEPA™, a PUFA formulation, may stabilise pancreatic ion channels to reduce hypoglycaemia in children with CHI.
Objectives: To investigate if MAXEPA supplements reduce hypoglycaemia risk in diazoxide-responsive CHI.
Methods: 13 patients (7 girls) with diazoxide-responsive CHI received MAXEPA 3 ml/day for 21 days in an open label pilot study. Glucose levels were monitored by subcutaneous continuous glucose monitoring systems (CGMS) pre-treatment, end of treatment and at follow- up. Adverse events were reported and insulin levels, liver function and lipid profiles were measured.
Results: Thirteen children with CHI, of median (range) age 5.9 (1.0;11.9) years and receiving 8.3 (5.0;12.0) mg/kg/day of diazoxide were recruited. CHI causing mutations were present in 4 (2 *ABCC8*, 1 *GCK*, 1 *HADH*) children. Seven children completed the trial as per protocol. In intention to treat analysis, overall mean (SD) CGMS glucose levels increased by a clinically insignificant increment of 0.1 mmol/l [5.26 (1.28) v 5.36 (1.14), $p< 0.001$]. However, in per protocol analysis (n=7), mean glucose levels increased by 0.4 mmol/l (8%). Importantly, the frequency of CGMS < 4 mmol/l, indicating risk of hypoglycaemia, was significantly less at the end of treatment than in the pre-treatment period [556 (7.0%) v 749 (10.1%), $p< 0.001$]. Except for one child with increased LDL cholesterol, all safety parameters were normal. Similar results were obtained when data was analysed as per protocol.
Conclusions: MAXEPA supplementation may reduce the risk of hypoglycaemia in children with CHI. The mechanism of action should be investigated and efficacy robustly tested in a more comprehensive clinical trial.

FC11-185 Congenital Hyperinsulinism

Successful treatment of five patients with severe hyperinsulinaemic hypoglycaemia with a novel therapy using mTOR inhibitor

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Background: Hyperinsulinaemic Hypoglycaemia (HH) is the most common cause of severe and persistent hypoglycemia in the neonatal period. The treatment of severe diazoxide unresponsive forms of HH involves pancreatectomy. Mammalian target of rapamycin (mTOR) is a protein kinase that regulates cellular proliferation. Overexpressed mTOR pathway has been suggested to play a role in the pathogenesis of diffuse HH. Recent reports have suggested successful use of mTOR inhibitors in insulinoma.
Objective and hypotheses: To evaluate the efficacy of mTOR inhibitor Sirolimus in infants and children with severe HH.
Methods: We recruited four infants with severe HH and a 6 year old child who had persistent hypoglycaemia unresponsive to diazoxide despite partial pancreatectomy. Treatment with diazoxide and octreotide were unsuccessful in all 4 infants who required high concentrations of intravenous dextrose and intravenous glucagon to maintain normoglycaemia. We commenced treatment with mTOR inhibitor and the dose was gradually increased based on serum concentration.
Results: Following treatment with mTOR inhibitor, all patients showed good glycaemic response. Intravenous dextrose fluids and glucagon were discontinued and oral feeds were established. 2 infants required small doses of octreotide. Two infants had maternal heterozygous ABCC8 mutation, one had homozygous ABCC8 mutation and one infant and the 6 year old child did not have any known mutation for HH. No side effects were noted on treatment. Immunostaining for mTOR expression in the pancreatic tissue is currently being undertaken.
Conclusions: We report, for the first time, the successful use of mTOR inhibitor in four infants and a child with severe form of HH. We suggest that mTOR inhibitors are a novel therapeutic option for severe HH thereby averting the need for surgery and its associated complications.

FC12-186 Mineral Metabolism

Functional rescue of inactivating and activating mutant CASRs by allosteric modulators

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Background and objective: Activating mutations in the calcium-sensing receptor (CASR) gene cause autosomal dominant hypoparathyroidism (ADH), and heterozygous inactivating CASR mutations cause familial hypocalciuiric hypercalcemia (FHH). Recently, there are has been a focus on allosteric modulators as rescue of mutant CASRs *in vitro*. In this study, the effect of allosteric modulators NPS R-568 and NPS 2143 to CASR mutants was studied.
Methods: We analyzed four activating mutations (S122C, P569H, I839T and A843E) and three inactivating mutations (A110T, R172G and R648X). Functional consequences for the Gi-MAPK pathway and cell surface expression of these mutants were determined. Furthermore, we studied the effect of NPS R-568 and NPS 2143 on the signal transduction activity and cell surface expression of each mutant CASR.
Results: The activating and inactivating mutations caused leftward and rightward shifts, respectively, in the dose-response curves of signaling pathway. NPS R-568 rescued the signal transduction capacity of two inactivating mutants without increasing cell surface expression levels. NPS 2143 suppressed the enhanced activity of the activating mutants without altering cell surface expression levels, A843E, which is a constitutively active mutant, was suppressed to a lesser degree.
Regarding the time course effect, maximal functional rescue of NPS R-568 is observed after 4-6hr treatment and the suppression of NPS 2143 was observed after 1hr treatment and lasted at 24hr.

Conclusions: Our results indicate that allosteric modulators could rescue the signal transduction of activating and inactivating mutant CASRs *in vitro*. These modulators may lead to the development of new approach to diseases caused by *CASR* mutations.

FC12-187 Mineral Metabolism

Anticalciuric effect of recombinant PTH in patients with activating mutations of the calcium-sensing receptor causing autosomal dominant hypocalcaemia-hypercalciuria (ADHH)

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Background: The majority of cases with hypoparathyroidism are well controlled under conventional treatment with calcium and vitamin D analogues. This treatment may be difficult to manage in patients with ADHH who have an increased risk of nephrocalcinosis and chronic renal insufficiency.
Objective and hypotheses: Evaluate the efficacy of $rPTH^{1-34}$ as an alternative to vitamin D analogue therapy for ADHH patients, in particular regarding the prevention of hypercalciuria and nephrocalcinosis.
Methods: Four patients, three toddlers (8, 18 and 30 months old; P1,P2,P3) and one young adult (19 years old, P4) with ADHH and documented CaSR heterozygous mutations, received $rPTH^{1-34}$ by continuous subcutaneous infusion via an insulin pump. The observed duration of therapy was 2 to 8 months (ongoing in all patients), with a mean daily dose of $rPTH^{1-34}$ 0.54, 0.57 and 0.37 µg/kg/day in the toddlers and 0.20 µg/kg/day in the adult patient. Additional treatments received were adjusted calcium supplements and cholecalciferol vitamin D.
Results: On rPTH therapy mean serum calcium levels increased in P1, P3 and P4 respectively from 1.4±0.15 to 2.1±0.25 mmol/L ($p< 0.05$), 1.5±0.3 to 1.8±0.5 mmol/L (ns) and from 2.2±0.3 to 2.38±0.3 mmol/L (ns). P2 showed a decrease in mean serum calcium from 2.13±1.8 to 1.95±0.1 mmol/L ($p< 0.05$). All four patients showed a decrease in mean urinary calcium excretion respectively from 1.8±0.9 to 0.5±0.5 mM/mM (ns), 2.4±0.5 to 1.1±0.4 mM/mM ($p< 0.05$), 1.3 to 0.6±0.26 mM/mM (ns) and from 4.8±3.4 to 3±0.9 mmol/L (ns) in P1, P2, P3 and P4.
Conclusions: rPTH allows the maintenance of serum calcium at near-normal levels in ADHH and correction of the clinically severe manifestations of hypocalcaemia. More importantly, even with near-normal blood calcium, rPTH had a significant anticalciuric effect, i.e. decreased significantly the urinary calcium excretion in ADHH patients, likely preventing or delaying renal damage.

FC12-188 Mineral Metabolism

Effects of the anti-rank ligand denusomab on adolescents with beta thalassaemia major-induced osteoporosis

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Background: Osteoporosis is common in patients with beta thalassemia major (BTM). Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL), recently used in treating osteoporosis.
Objective: To evaluate the efficacy and safety of anti RANK ligands on the biochemical and radiological parameters of bone mineralization in patients with BTM-induced osteoporosis.
Methods: Eight adolescents with BTM and osteoporosis were evaluated biochemically by checking their serum calcium, phosphorus, bone specific alkaline phosphatase, creatinine and type 1 collagen carboxy telopetide (1CCT) with the use of ELISA at baseline and 12 months after starting Denosumab 60 mg subcutaneously twice yearly for a year. Fasting serum samples were collected before and 1 and 6 months after the injection. Radiological evaluation was done by DEXA scan (using WHO criteria) and biochemical evaluation of bone turnover markers included bone specific alkaline phosphatase and 1CCT.
Results: Denosumab therapy for a year was associated with a significant increase in bone mineral density of 9.2% (95% CI, 8.2 to 10.1) at the lumbar spine and 6.0% (95% CI, 5.2 to 6.7) at the total hip. Denosumab treatment decreased serum TICCT levels by 50% at 1 month and normalized them in all patients at 1 year. Serum Ca, PO4 and PTH did not differ before vs after therapy. Significant correlations were found between bone mineral density T score before and 1year after Denosumab in vertebral ($r = = 0.642$, $p < 0.001$) and both hips ($r = 0.69$ respectively $p < 0.001$). Pain in the extremities and nausea occurred in a patient.
Conclusions: In adolescents with BTM and osteoporosis Denosumab therapy for a year significantly decreased bone resorption and increased bone mineral density and was associated with reduction in bone turnover.

FC12-189 Mineral Metabolism

The effect of nutritional rickets on bone mineral density

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Background: Nutritional rickets causes impaired mineralization of growing bone. The effect of nutritional rickets on bone mineral density (BMD) has not been established.
Objective and hypotheses: We hypothesized that BMD would be lower in children with rickets than in healthy control children. We expected that the reduction in BMD would be more pronounced in the distal forearm near the growth plate than in the proximal 1/3 forearm.
Methods: Nigerian children with radiographically-confirmed nutritional rickets were compared with a reference group of control children without rickets from the same community. Forearm bone density measurements were performed in all children with DXA. Age, sex, and height-adjusted bone density parameters were compared between children with rickets and control subjects.
Results: A total of 264 children with rickets (ages 12-120 months) and 647 control children (ages 11-123 months) were included. In multivariate analyses controlling for height, age, and sex, rickets was associated with a 4.2% greater bone area (BA) and 7.5% lower BMD of the distal forearm compared with controls ($p< .001$). The effects of rickets on the proximal 1/3 radius and ulna were more pronounced with a 17% greater BA and 20% lower BMD than controls ($p< .001$). In children with rickets, bone density parameters were not related to dairy product intake, radiographic severity score, serum calcium, phosphorus, alkaline phosphatase, or 25-hydroxyvitamin D values. A positive association of distal BMD with radiographic severity score was interpreted as an artifact of more proximal identification of the distal bone edge by densitometry.

Conclusions: Rickets results in increased BA and reduced BMD, which are more pronounced in the proximal than the distal forearm. These findings are consistent with generalized osteoid expansion and impaired mineralization.

FC12-190 Mineral Metabolism

Patterns of renal distal tubule PTH sensitivity in subtypes of pseudohypoparathyroidism

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Background: In the distal tubule (DT), PTH stimulates calcium reabsorption following binding to its receptor PTHR1 and stimulation of the adenylcyclase-cAMP-PKA pathway. Two proteins encoded by the GNAS locus couple the activated receptor to adenylcyclase: Gsalpha, with biallelic expression in the DT, and XLsalpha, paternally expressed. The contribution of these proteins, in particular XLsalpha, to PTH effect on calcium reabsorption in pathophysiology is not known.
Objective and hypotheses: The aim of this study is to attempt to decipher these contributions through the analysis of a series of patients with either PTH absence (hypoparathyroidism, HP), or resistance (pseudohypoparathyroidism, PHP) with respectively normal and abnormal active Gsalpha and/or XLsalpha transcript expression.
Subjects and methods: We measured biological phosphocalcic parameters in 28 patients with HP, 19 with PHPIa, 22 with sporadic (s)PHPIb, and 9 with familial (f)PHPIb. The pattern of active Gsalpha/XLsalpha transcript expression in these patients is as follows: HP ("normal" pattern) 2/1; PHPIa 1/1; sPHPIb: 2/2; fPHPIb: 2/1.
Results: At diagnosis, calcemia and phosphatemia were similar in s+f PHPIb and HP and respectively lower and higher than in PHPIa. PTH was higher in s+f PHPIb than in PHPIa. When treated (1alfa-OHD), calciuria was within the normal range in PHPIa and fPHPIb, and increased in sPHPIb.
Conclusions: PTH resistance is more severe in s+f PHPIb than in PHPIa at diagnosis. The expression of 2 XLsalpha alleles (sPHPIb) is associated with an increase in urinary calcium excretion. These results suggest that, in the tubules, XLsalpha expression does not rescue Gsalpha deficient signaling and may contribute to PHP clinical heterogeneity.

FC12-191 Mineral Metabolism

Comprehensive genetic analyses of primary hypoparathyroidism using next-generation sequencing

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Background: *AIRE*, *CASR*, *GATA3*, *GCM2*, *TBCE* and *PTH* are responsible genes for primary hypoparathyroidism (PH). To date, no study has been reported analyzing all the six genes comprehensively in PH patients.
Objectives: To determine the genetic defect and to characterize the identified novel mutations in PH patients.
Subjects and methods: The study subjects were 17 non-consanguineous Japanese PH patients without 22q11.2 deletion. Mutations in the six genes were screened using next-generation sequencing (NGS) and validated by PCR-direct sequencing. Copy number variations were analyzed by PCR-direct sequencing, array CGH and NGS. Putative deletion was confirmed by digital droplet PCR. The identified novel mutants were characterized by the followings: 1. *in silico* PyMOL molecular graphics system for *GATA3* and 2. luciferase reporter assay, western blot analysis, nuclear localization study and EMSA using PT-r (rat parathyroid) cell for *GCM2*.
Results: We identified 8 sequence variations, including one recurrent one in *CASR*, four in *GATA3* (one novel C431Y), and three novel in *GCM2* (R367fs, T370M, and exon1 deletion sized 3.6 kb). The *GCM2* deletion could be detected by NGS, not by PCR-direct sequencing or array CGH. We confirmed the deletion by digital droplet PCR. C431Y in *GATA3* was predicted to impair Zinc finger structure by PyMOL. Functional studies of R367fs and T370M in *GCM2* demonstrated that both resulted in a reduction of gene transactivation, while mutant proteins were localized at the nucleus and retained ability to bind the GCM motif.
Discussion and conclusions: All novel sequence variations in *GATA3* and *GCM2* were verified to be causative mutations. Seven out of 17 patients had mutations in the six genes, suggesting relatively common single gene mutations in PH. Additionally, NGS might be more sensitive to detect small deletion than PCR-direct sequencing and array CGH.

FC13-192 Endocrine Oncology

Differential expression profile of miRNAs in paediatric non-neoplastic adrenal tissue, metastatic and non-metastatic paediatric adrenocortical tumors

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Background: Although pediatric adrenocortical tumors (ACTs) are very rare malignancies (0.2% of pediatric tumors), in Southern of Brazil their incidence is 10-15 times higher and present poor prognosis in metastatic disease. Abnormal miRNAs expression has been shown to play an important role in development and progression of different neoplasias and its role in pediatrics ACT is little known.
Objective and hypotheses: The present study aimed to evaluate the miRNAs signature in samples from pediatric patients with ACTs.
Methods: We investigated the global expression of miRNAs in 37 samples of pediatric ACTs compared to 9 pediatrics non-neoplastic adrenal cortex using the Human miRNA Microarray Kit (V3-Agilent), with 955 microRNA represented. The expression levels of 4 miRNA were validated by qRT-PCR using TaqMan probes.
Results: A significant modulation of the expression was found in 128 miRNAs with a $P < 0.05$ (*false discovery rate* corrected) and fold-change $\geq |5|$. We found 10 miRNAs down regulated and 118 up regulated in pediatric ACT compared to non-neoplastic samples. Differential miRNA expression was also observed between the ACTs presenting metastasis at diagnosis compared to those without metastasis: 9 down and 19 up regulated. These miRNAs have predicted/validated target genes involved in apoptosis, antigen processing and presentation and several signaling pathway as mTOR, ErbB, Insulin, Shh, Wnt, TGFB, VEGF, GnRH, Notch and p53. Abnormal miRNA expression was confirmed by qRT-PCR to let-7e, miR-128a and miR-196b (up regulated) and miR-92a (down regulated) in ACTs compared to control samples.
Conclusions: Our findings suggest a potential role of miRNAs in tumorigenesis and progression, which can contribute to a better understand and management of pediatric ACTs.

FC13-193 Endocrine Oncology

Correlations between gene expression of *IGF1R* and *IGF2* and WNT/B-catenin pathways in paediatric adrenocortical tumors (ACTs)

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Background: Alterations in IGF system and WNT/b-catenin pathway have been found in pediatric and adult ACTs. Recently, studies provided evidences that IGF signaling modulates the canonical WNT pathway at the level of b-catenin, but little is known about this interaction in cancer cells, especially in ACTs.
Objective and hypotheses: To investigate correlations between *IGF1R* and *IGF2* and WNT/B-catenin pathways in pediatric ACTs.
Methods: The correlations between the mRNA expression values of IGF system genes and WNT/b-catenin components were determined by the Spearman correlation coefficient (rho) in 57 pediatric ACTs. Non-neoplastic adrenal samples (n=19) were used as controls. Gene expressions were analyzed by RT-qPCR using TaqMan probes by the $2^{-\Delta\Delta Ct}$ method.
Results: ACT presented increased expression of *IGF2*, *CTNNB1*, *WISP2* and underexpression of *DKK3*, *SFRP1*, *AXIN1* and *MYCC* when compared to normal samples. Higher survival was associated with underexpression of *IGF1R*, *SFRP1*, *WNT4* and *TCF7* ($P < 0.05$). A significant positive correlation was found between the *IGF1R* gene expression and the target gene of WNT/b-catenin pathway *MYCC* (rho=0.529; $P < 0.001$). Two inhibitors of WNT/b-catenin were also positive correlated with *IGF1R*: *AXIN1* (rho=0.375; P=0.009) and *SFRP1* (rho=0.314; P=0.034). In addition, the major ligant *WNT4* presented a significant negative correlation with *IGF1R* (rho=-0.316; P=0.031). Considering the gene expression of *IGF2*, we observed a positive correlation of this ligant with the WNT/b-catenin target gene *WISP2* (rho=0.311; P=0.036). It was also found a positive correlation between *IGF2* and the gene expression of the main mediator of WNT/b-catenin pathway, the *CTNNB1* (rho=0.289; P=0.049).
Conclusions: We observed significant correlations of components of WNT/b-catenin signaling and the receptor *IGF1R* in our pediatric ACTs samples, suggesting that interactions between both pathways can be related to carcinogenesis process.

FC13-194 Endocrine Oncology

Factors influencing prognosis of stage I and II adrenocortical tumor in children and adolescents: experience of 101 cases

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Background: Childhood adrenocortical tumor (ACT) is rare. However, in Southern Brazil its incidence is 15 times greater than elsewhere in the world. The germline mutation R337H of TP53 gene was described in 2001 in near 90% of patients in the State of Parana. Tumor staging, according to Sandrini et al. is used to establish prognosis and therapeutic strategy. Besides staging, other parameters could be considered to optimize the approach of any child with ACT.
Objective: To review clinical and follow up data of children with stages I and II ACT.
Hypotheses: Other parameters besides tumor staging are associated with prognosis.
Methods: Review of files of patients with ACT followed in the same institution in the period of 1966-2012, with emphasis on epidemiology, clinics, treatment and recurrence.
Results: Out of 144 patients, 101 were classified as stage I (n=71) and II (n=40). Twenty-three had recurrence (2 of stage I) and were treated with chemotherapy (Berrutti's protocol). Age at diagnosis (p=0,017), time of disease (p=0,016) and survival (p=0,009), spillage during surgery ($p < 0,05$), adherence to adjacent structures (p=0,03) and venous thrombus (p=0,05) were significantly different between patients with and without recurrence. Gender, clinical presentation and the presence of germline R337H TP53 mutation did not influence prognosis.
Conclusions: Based on this casuistic, staging and the parameters herein reviewed should be taken together in every case of a child with ACT to establish a prognosis and to plan treatment.

FC13-195 Endocrine Oncology

The Use of ^{123}I in diagnostic radioactive iodine uptake scans in children with differentiated thyroid carcinoma and metastatic disease: a case series at a single academic center

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Background: Children with thyroid cancer are at greater risk for metastatic lung disease compared to adults. Radioactive iodine (RAI) type and dose in diagnostic scanning has not been well studied in children with thyroid cancer. Adult studies have shown that ^{123}**I**, which emits γ but not β radiation and does not carry the risk of "stunning", is as effective as ^{131}**I** in detecting metastatic disease.
Objective and hypotheses: To describe our institution's experience using ^{123}**I** in diagnostic RAI total body scans in children with differentiated thyroid carcinoma and whether an increased dose of ^{123}**I** from 2mCi to 3mCi results in improved detection of metastatic disease.
Methods: All patients with differentiated thyroid carcinoma who completed diagnostic scanning followed by RAI therapy at our institution over the past 8 years were included in this retrospective study. One radiologist interpreted all scans. Patients were either withdrawn from thyroid hormone replacement 2 weeks prior to scan or given thyrogen® (0.9 mg IM daily for 2 days) to stimulate TSH. Serum thyroglobulin levels were drawn on or within a few days of RAI dosing.
Results: 33 patients (7 male, mean age 13.3 years) had 37 sets of scans. For diagnostic RAI scanning, 5 patients received 2mCi ^{131}**I**, 21 received 2mCi ^{123}**I**, and 11 received 3mCi ^{123}**I**. Diagnostic and treatment scans had consistent findings in 76% of cases. Metastatic lung disease, confirmed by ^{131}**I** treatment scan, occurred in 33% of patients, yet was detected by ^{123}**I** diagnostic scan in only 22% of cases. Increasing the diagnostic RAI dose of ^{123}I from 2mCi to 3mCi did improve detection of metastatic lung disease. Thyroglobulin level was a reliable indicator of metastatic disease in 65% of cases.
Conclusions: Use of ^{123}**I** for diagnostic scanning in children with differentiated thyroid cancer is safe and has the advantage of decreased radiation exposure and avoidance of "stunning". However, there can be missed detection of metastatic lung disease.

FC13-196 Endocrine Oncology

Disease- and treatment-related factors implicated in late neuroendocrine morbidity after paediatric optic pathway gliomas: a preliminary multivariate analysis of 128 patients over 30 years

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Background: Low-grade gliomas (LGGs) are the commonest benign childhood brain tumour and typically affect the optic pathway and diencephalon, thus potentially causing serious neuroendocrine deficits from tumour and/or treatment.
Objective and hypotheses: In the absence of any major studies, we sought to evaluate patient-, disease- and treatment-related risk factors for endocrine morbidity in a large single-centre cohort treated over 30 years.
Methods: Retrospective case note analysis of the first 128/225 randomly audited patients diagnosed with optic pathway and diencephalic LGGs between 1980-2010 at Great Ormond Street Hospital by multivariate regression.
Results: Patients were of median age 5.15 (0.18-15.07) years at diagnosis and followed up for a median of 7.32 (0.04-26.12) years. 5-year overall, progression-free and endocrine event-free survival (EEFS) were 96.4%, 60.5% and 40.3% respectively, with EEFS falling up to 15 years from diagnosis, being independently reduced by hypothalamic involvement (p=0.00) more than radiotherapy (p=0.01). The number of deficits was increased by radiotherapy (p=0.00), surgery (p=0.03) and the presence of diencephalic syndrome (p=0.04). GH deficiency was commonest (38.3%), followed by precocious puberty (19.5%), ACTH deficiency (14.8%), TSH deficiency (10.9%), LH/FSH deficiency (10.2%) and hyperprolactinaemia (10.2%). 12/13 patients with posterior pituitary dysfunction were post-operative (10 post-biopsy/shunt procedures only). At last follow-up, 35.2% were obese, with hypothalamic involvement being the only significant predictor (p=0.01).
Conclusions: This long-term multivariate analysis of endocrine morbidity in LGG survivors provides new evidence to suggest that hypothalamic involvement is more predictive of the onset of endocrinopathies than irradiation, and challenges the perception that surgery is less neurotoxic, as even minor surgical intervention to the diencephalon can result in significant posterior pituitary dysfunction.

FC13-197 Endocrine Oncology

Local deficiency of Insulin-like growth factor-I receptor (IGF-IR) modulates the initial steps of experimental pheochromocytoma (Pheo) development

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Background: We have shown that circulating IGF-I has a critical role in maintaining tumor phenotype and survival of already transformed pheochromocytoma cells (MPC4/30), and is required for the initial establishment of these tumors.
Objective and hypotheses: To investigate the role of the local IGF-I/IGF-IR system that is present in the tumor microenvironment including endothelial cells, fibroblasts and extracellular matrix.
Methods: We used a murine model of pheochromocytoma by sc injection of $1x10^6$ MPC4/30 cells in heterozygous IGF-IR knockout mice ($IGF\text{-}IR^{+/n}$).
Results: We found that the time of tumor appearance was delayed in $IGF\text{-}IR^{+/n}$ group (n=53) compared to control $IGF\text{-}IR^{+/+}$ mice (C,n=79) [6 vs 5 weeks,Hazard Ratio:0.27;95%CI:0.16- 0.46]. Additionally, 9.43% of $IGF\text{-}IR^{+/n}$ mice did not develop tumor ($p< 0.0001$,Logrank Test,$IGF\text{-}IR^{+/n}$vs.C) while proliferation assessed by BrdU incorporation, vascularization measured as the number of positive endothelial cells for Von Willebrand factor and tumor volume did not differ between the groups. To evaluate the impact of IGF-IR deficiency in the initial steps of pheo development, primary fibroblast cultures from $IGF\text{-}IR^{+/n}$ and C mice were used to generate conditioned media (CM) and differential matrix on which MPC4/30 were seeded. *In vitro* MPC4/30 cell proliferation was higher when cultured with CM from C murine fibroblasts (20 ± 1 vs 13 ± 2 $x10^4$cells,C vs $IGF\text{-}IR^{+/n}$,day 7,$p= 0.025$). Moreover, similar results were obtained when MPC4/30 cell were cultured in differential matrix generated by C murine fibroblasts(23 ± 2 vs $17\pm1x10^4$cells,C vs $IGF\text{-}IR^{+/n}$,day 5,$p< 0.05$) with a significantly increased of BrdU uptake on day 5 ($38\pm2\%$ vs $28\pm2\%$ positive nuclei,C vs $IGF\text{-}IR^{+/n}$,$p < 0.005$).
Conclusions: Our data suggest that IGF-I through its type 1 IGF-IR may be involved in early stages of tumor establishment, contributing to tumor cells anchorage by interaction with both matrix and soluble factors produced by tumor microenvironment fibroblasts.

FC14-198 Perinatal and Neonatal Endocrinology

Placental expression of *SPRY2:* relation to maternal metabolism and placental growth

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Background: SPROUTY2 (SPRY2) is a membrane-associated protein with inhibitory roles in tissue outgrowth. In placenta, *SPRY2* is expressed by placental macrophages to limit placental villous expansion. Genetic variation in *SPRY2* has been recently associated to body fat distribution and susceptibility to type 2 diabetes.
Objective and hypotheses: We assessed whether maternal metabolism and placental expression of macrophage-derived cytokines are related to placental *SPRY2* and whether the expression of this gene relates to placental size.
Methods: Expression of *SPRY2* and of proinflammatory *TNFα, MMP2* and *CD163* were quantified at birth in placentas from 250 pregnant women [200 control women with normal pregnancies, 25 women with gestational diabetes (GDM; NDDG criteria) and 25 women delivering small-for-gestational-age (SGA) infants]. Maternal fasting serum C-peptide, post-load glucose and HMW-adiponectin were assessed between 24 and 28 weeks of gestation. Placentas and newborns were weighed at delivery.
Results: Placental size increased in parallel to placental *SPRY2, TNFα, MMP2* and *CD163* from women delivering SGA infants (lower size and expression) through control women (average size and expression) to GDM women (higher size and expression; all $p< 0.0001$). In control women, higher placental *SPRY2* was related to lower HMW-adiponectin and higher C-peptide, post-load glucose and placental expression of *TNFα, MMP2* and *CD163* ($p< 0.05$ to $p< 0.0001$). In multivariate analysis, placental *CD163* and maternal C-peptide were independently related to placental *SPRY2* ($p< 0.0001$ and $p=0.01$, respectively).
Conclusions: These results suggest that placental SPRY2 is involved in the orchestrated regulation of placental growth and maternal metabolism.

FC14-199 Perinatal and Neonatal Endocrinology

Placental expression of *ATG7,* an autophagy gene, associates to weight partitioning among the mother, the placenta and the fetus

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Background: Autophagy or autophagocytosis is the process of breaking down cellular components to ensure cellular survival during starvation. During development, autophagy may have a role in placentation and is increased in placentas from patients with preeclampsia.
Objective and hypotheses: To assess whether maternal metabolism is related

to placental *ATG7* and whether the expression of this gene relates to feto-placental weight.
Methods: *ATG7* expression (real-time PCR) was quantified in placentas from 145 pregnant women who were recruited in a setting of prenatal primary care, of whom 100 were lean and 45 were overweight (pre-pregnancy BMI >25). Maternal fasting lipids and C-peptide, HbA1c and high molecular weight (HMW) adiponectin were assessed between 24 and 28 weeks gestation. Placentas and newborns were weighed at birth. Infants were all born at term with normal weights.
Results: Fetal and placental size and placental *ATG7* were higher in overweight *vs.* lean women ($p< 0.05$). In overweight women, placental *ATG7* expression was associated with higher triglycerides (TG), C-peptide, HbA1c and lower HDL-cholesterol and HMW-adiponectin, and with increased placental weight and decreased fetal-to-placental-weight ratio (all $p< 0.05$ to $p< 0.001$). In these women, placental *ATG7* expression was independently associated with TG ($\beta= 0.394$, $p=0.005$) and HbAc1 ($\beta= 0.436$, $p=0.002$) and explained 5% of placental weight variance ($\beta=0.249$, $p=0.017$) and 11% of the variance of fetal-to-placental-weight ratio ($\beta= -0.352$, $p=0.006$).
Conclusions: Placental expression of *ATG7* may orchestrate the weight partitioning among the pregnant mother, the placenta and the fetus.

FC14-200 Perinatal and Neonatal Endocrinology

Prematurity should not prevent genetic testing for neonatal diabetes

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Background: Hyperglycaemia in premature infants is usually thought to reflect inadequate pancreatic development rather than neonatal diabetes due to a monogenic cause. However, there have been no studies to investigate monogenic forms of neonatal diabetes in preterm babies.
Objective and hypotheses: We aimed to assess the clinical characteristics and genetic aetiology of preterm patients with neonatal diabetes.
Methods: We studied an international cohort of 750 patients with diabetes diagnosed before 6 months of age. We compared the genetic aetiology and clinical characteristics of 146 patients born prematurely (< 37 weeks) and compared them to 604 born ≥37 weeks.
Results: A defined genetic aetiology was found in 97/146 (66%) preterm infants rather than 501/604 (83%) born ≥37weeks, $p< 0.0001$. Chromosome 6q24 imprinting abnormalities and *GATA6* mutations occurred more commonly in preterm than term infants (6q24: preterm 27% v term 12%, $p=0.0001$; *GATA6*: 9% v 2%, $p=0.003$) whilst mutations in *KCNJ11* were less common (21 v 34%, $p=0.008$).
The preterm patients with an identified mutation were diagnosed later than those without an identified mutation (35(34-36) weeks [median(interquartile range)] v 31(28-36) weeks, $p< 0.0001$). No difference was seen in other clinical characteristics of preterm patients with and without an identified mutation (age of presentation (1.0(0.1-4.0) v 0.7(0.1-3.5), $p=0.99$), birthweight SDS (-1.28(-2.27 -0.43) v -1.06(-1.98- -0.20), $p=0.48$), time to referral for genetic testing (19(4-212) v 8(4-42), $p=0.10$).
Conclusions: Patients with neonatal diabetes due to a monogenic aetiology can be born pre-term, especially those with 6q24 abnormalities or *GATA6* mutations. A genetic aetiology is more likely in patients with less severe prematurity. Prematurity should not prevent referral for genetic testing as 37% have a potassium channel mutation that predicts improved glycaemic control with sulphonylurea therapy.

FC14-201 Perinatal and Neonatal Endocrinology

Hormone levels in extreme prematurity: establishment of gestational appropriate reference intervals for FSH, LH and prolactin

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Background: Preterm infants, particularly those who are extremely premature, frequently have endocrine testing, due to multiple health issues including resistant hypotension, need for prolonged ventilatory support or genital appearance. Immaturity of the endocrine system and its potential impact on morbidity is the subject of numerous studies. Reports suggest significant differences in serum levels of pituitary hormones in extremely preterm compared to older preterm and full term infants. Little normative data is available for this cohort.
Objectives: To develop reference intervals for three pituitary hormones measured in preterm infants.
Methods: Blood was collected from 249 (129 male,120 female) extremely preterm infants, born between 24 and 35 weeks gestation, at 2-3 week intervals, to 36 weeks gestational age. No infant in this cohort had ambiguous genitalia or other endocrine abnormality. Samples (median: 3 per neonate) were collected. Serum was analysed for prolactin, FSH and LH by automated electrochemiluminescence immunoassay (Roche Cobas 8000 - E602). Infants not surviving beyond the equivalent of term were excluded from statistical analysis.
Results: Reference intervals were established with samples from 230 of the 249 extremely preterm infants; representing 521 (267 male and 254 female) samples analysed throughout the first six weeks of life. Distribution was non-Gaussian. Initial assessment established the 95% central range for each pituitary hormone. For male extremely preterm infants the ranges are: prolactin 605-4798 mIU/L; FSH 0.2-4.7 IU/L; and LH 0.3-8.3 IU/L. The female extremely preterm infant ranges are: prolactin 666-5854 mIU/L; FSH 5.7->174 IU/L; and LH 0.4-167 IU/L.
Conclusions: Utilisation of these three pituitary hormones measured in the first six weeks of life for infants born < 32 weeks' gestation will permit correct interpretation of results for this population and reduce risks of incorrect diagnosis due to misinterpretation of data.

FC14-202 Perinatal and Neonatal Endocrinology

Involvement of gonadal control in gonadotropin secretion in infancy

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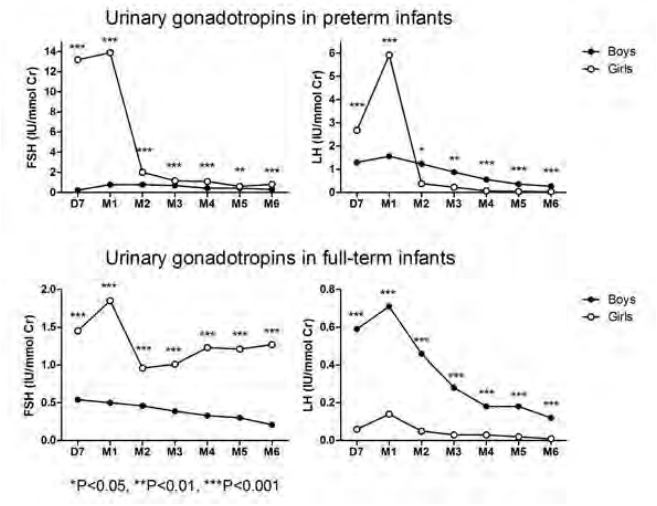
Background: The postnatal gonadotropin surge is sexually dimorphic: FSH levels predominate in girls and LH levels in boys. In premature infants, especially in girls, postnatal gonadotropin levels are several fold higher than in term infants.
Objective: To evaluate if the gonadal hormones contribute to this sex difference in gonadotropins in infancy.
Methods: In 58 full term (FT, gestational age (GA) >37 weeks, 29 girls) and 67 preterm infants (PT, GA 24.7-36.7, 34 girls), urinary LH, FSH, estradiol (E2) and testosterone (T) were measured monthly from one week (D7) to six months of age (M1-M6) and serum inhibin B (inhB) at D7 and M3.
Results: FSH levels were lower in boys than girls (Figure) and were negatively correlated with inhB levels at D7 and M3 (rho -0.62 and -0.64 respectively, $P< 0.001$). In FT infants, LH levels were higher in boys than in girls but in PT infants, girls had higher levels than boys until M2, when the levels in girls decreased below the levels in boys.
The abrupt decrease in LH and FSH levels in PT girls was associated with a

significant increase in both E2 (P< 0.001) and inhB (P< 0.001) levels.
T levels were high in PT boys after birth but in PT girls, E2 levels remained low until term age and then increased. At M3, E2 and inhB correlated positively in girls (rho 0.43, P= 0.001).
Conclusions: Sexually dimorphic changes in postnatal gonadotropin levels in PT infants reflect the maturational differences in gonadal development. Insufficient ovarian negative feedback effects on pituitary gonadotropin secretion might explain the highly elevated postnatal FSH and LH levels in PT girls.



[Figure]

FC14-203 Perinatal and Neonatal Endocrinology

Transient postnatal gonadal activation regulates linear growth in infants

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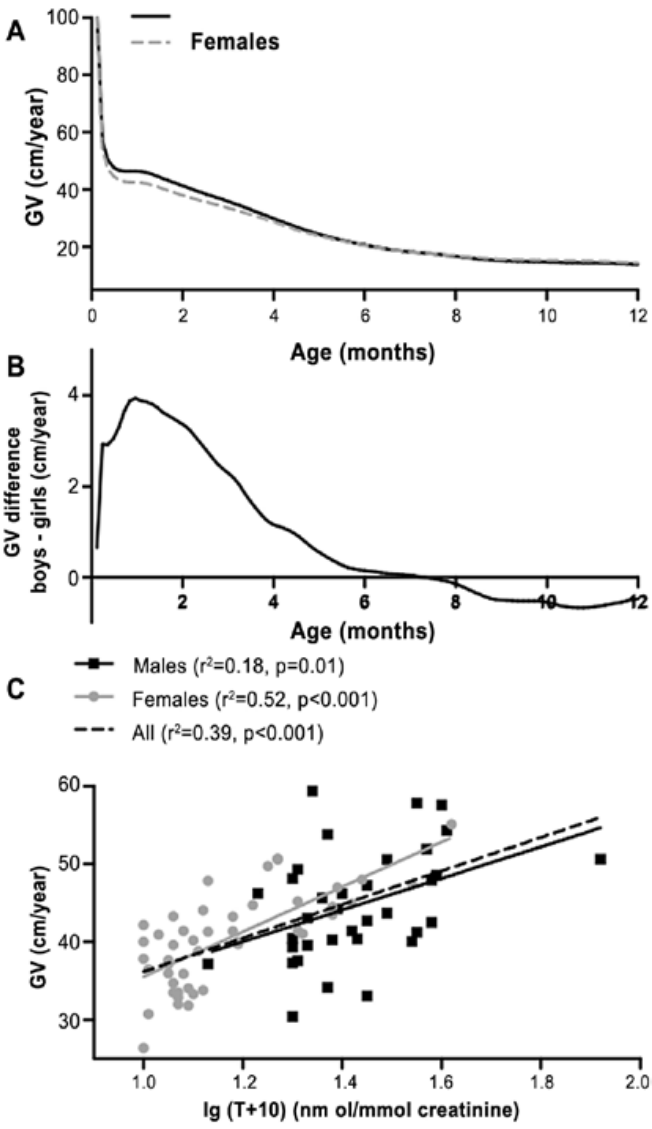
Background: Linear growth is primarily regulated by the GH-IGF-1 axis. During puberty, growth velocity (GV) is greater in boys than in girls mainly due to different sex steroid milieu, but the role of sex steroids in the regulation of growth has not been substantiated at any other age.
Objective and hypotheses: We hypothesized that analogously to puberty, testosterone surge during the transient postnatal gonadal activation regulates growth.
Methods: We assessed linear growth of 12,074 healthy children and differences in GV between sexes during the 1st year of life. To associate the differences in GV with sex steroids during the postnatal gonadal activation, a longitudinal cohort study was conducted with 84 preterm and full term infants (45% boys). Growth and urinary creatinine corrected testosterone concentration (T) were followed monthly from birth to 6 months of age. The relationship between T and modeled GV was analyzed with correlation analyses and linear mixed models, in which possible confounding factors such as gestational age and relative birth size could be controlled.

Results:



[Figure 1]

The decelerating GV after birth had a short plateau coinciding with the peak of postnatal gonadal activation at 1 to 2 months of age (Fig 1A). During this period, GV was 3.9 cm/y higher in boys than girls (Fig 1B).
We identified a positive association between T and GV, which was strongest at 2 months of age (r^2=0.39, p< 0.001) (Fig 1C). The association was significant even after adjustments for confounding factors.
Conclusions: The results provide a new insight into the regulation of growth in infants and elucidate a novel biological role for the transient postnatal gonadal activation.

FC15-204 Adipose Tissue

Peroxiredoxin 3 regulates adipogenic differentiation and glucose uptake in human adipocytes

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Introduction: Peroxiredoxin 3 (Prdx3) is a thioredoxin dependent peroxidase localized in mitochondria. The expression of *Prdx3* is upregulated during adipogenic differentiation of 3T3-L1 cells. Furthermore, Prdx3 mRNA is decreased in obese adipose tissue.
Objective: Our aim was to elucidate the function of Prdx3 in human adipocytes.
Methods: Human SGBS preadipocytes and human primary preadipocytes were used as model systems. Prdx3-deficient cells were generated using the BLOCK-iT Lentiviral shRNA System (Invitrogen). Gene expression was studied by qPCR and western blot.
Results: The expression of *Prdx3* was upregulated during adipogenesis in SGBS cells and human primary preadipocytes indicating its physiological relevance in humans. We generated SGBS preadipocytes stably overexpressing Prdx3 shRNA achieving a knockdown by approx. 80%. Interestingly, adipogenic differentiation was completely inhibited in Prdx3-deficient cells as seen by absence of lipid accumulation, while control cells displayed a differentiation rate of 80%. This was paralleled by complete inhibition of adipogenic marker gene expression, i.e. PPARgamma, leptin and adiponectin.
We performed knockdown of Prdx3 in adipocytes to study its role on metabolic processes. Insulin-stimulated glucose uptake was inhibited by ~20% compared to control cells. The mRNA expression of Glut-4 was not significantly altered in Prdx3-deficient adipocytes. We currently study insulin-stimulated phosphorylation of intracellular kinases to elucidate the molecular mechanism leading to alterations in glucose uptake.
Conclusion: Prdx3 deficiency leads to inhibition of adipogenic differentiation and inhibition of glucose uptake. Both processes are stimulated by insulin. We therefore conclude that Prdx3 is an important regulator of insulin sensitivity in human preadipocytes and adipocytes.

FC15-205 Adipose Tissue

Resveratrol inhibits inflammation-induced fibrosis in human adipocytes

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Background: Obese adipose tissue is infiltrated by macrophages and shows signs of fibrosis ultimately leading to insulin resistance. A supplementation with resveratrol can reverse the metabolic disturbances in human obesity, in part by mimicking the effects of caloric restriction.
Objective: We hypothesized that the beneficial effects of resveratrol might be mediated by its anti-fibrotic effect on adipocytes.
Methods: To mimic adipose tissue fibrosis we incubated SGBS adipocytes with THP-1 macrophage conditioned medium (MacCM) in the presence or absence of 100 µM resveratrol. Fibronectin (FN) and collagen 1A1 (col1A1) were studied as fibrosis markers.
Results: Treatment with 10% MacCM resulted in upregulation of FN (~3.5 fold) and col1A1 (~2.1 fold) mRNA in adipocytes. The same effect was detected on the protein level. This was completely inhibited by coincubation with resveratrol. In order to elicudate the molecular pathway involved, we took advantage of small molecule inhibitors targeting either Sirt1 or PI3K. Interestingly, inhibition of Sirt1 with sirtinol (10 µM) did not interfere with the effects of resveratrol, indicating that Sirt1 is not involved in mediating the effects of resveratrol on adipocyte fibrosis. Inhibition of PI3K with Ly294002 (20 µM) however, prevented the MacCM-induced upregulation of FN and Col1A1 mRNA expression. Western blot analysis revealed that MacCM induced phosphorylation of Akt and its downstream targets GSK3β, FOXO1 and mTOR, which was again inhibited by resveratrol.
Conclusion: We show that resveratrol inhibits the inflammation-induced development of fibrosis in adipocytes, mediating its anti-fibrotic effect by involving the PI3K/Akt pathway. Taken together, our results demonstrate that resveratrol has health beneficial effects on human adipocytes. Preventing proinflammatory conditions and fibrosis in adipose tissue might be a useful strategy to prevent the development of insulin resistance in the obese state.

FC15-206 Adipose Tissue

Adipose tissue selective TSH receptor knockout alters the gene expression in brown but not in white adipose tissue

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Background: It has been suggested that thyrpotropin (TSH) plays an important role in adipose tissue metabolism and development. Its actions are mediated via binding to TSH receptor (TSHr), which is expressed in white and brown adipocytes. In white adipocytes the lipolytic effect of TSH has been demonstrated both in mice and young infants. The impact of TSH - TSHr interaction on gene expression during physiological conditions in vivo in these two types of adipocytes remains unclear.
Objective and hypotheses: We investigated the tissue expression of selected genes involved in white adipose tissue (WAT) and brown adipose tissue (BAT) metabolism in a TSHr adipose tissue specific knockout model.
Methods: TSHr adipose tissue specific knockout mice were phenotypically characterized in terms of Body weight, adipocyte size and thermoregulation. Selected gene expression including, hormone sensitive lipase (HSL), peroxisome proliferator-activated protein gamma (PPARγ), β3 adrenergic receptor (ADRB3) were studied using quantitative real time polymerase chain reaction when the animals were 8 wks old.
Results: No differences in weight between KO and WT mice. White adipocytes were larger in KO than in WT mice (mean ± SEM 52.70 ± 0.18 µm and 48.70± 0.19 µm, P< 0.001). In mice lacking TSHr in brown and white adipocytes, BAT express lower levels of HSL (80 % of WT), β3 adrenoceptor (80 % of WT), and adipocyte nuclear receptor PPARγ (85% of WT) than wild type litter mates. In contrast, no significant differences in expression level were observed in WAT obtained from the same animals.
Conclusions: This is the first demonstration that the TSH-TSHr interactions in brown adipocytes in vivo have a prominent effect on the expression of genes involved in BAT differentiation and metabolism. In white adipocytes the metabolism is altered without any identified alteration of gene expression indicating that the effect of TSH in WAT is restricted to a reduced lipolysis leading to increased fat cell size.

FC15-207 Adipose Tissue

Exposure to increased androgens during early development modifies circulating adipokine levels and adipokine expression in visceral adipose tissue in adult female rats

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Background: Adipose tissue distribution and metabolic function differ between normal males and females, causing distinct propensities towards metabolic disease. As polycystic ovary syndrome is associated with androgen excess, modifications in adipose tissue physiology could be involved in the increased weight gain and secondary complications observed in this condition.
Objective and hypotheses: We hypothesized that exposure of females to excess androgen during development modifies both the amount of adipose tissue in adulthood and its production of cytokines thus increasing the possibility of metabolic abnormalities.
Methods: On postnatal day (PND) 1 female rats were injected with testosterone (208mg/kg) or vehicle, while males received vehicle. All rats were killed on PND90. Body weight, length, fat pads, glycemia, circulating cytokines and mRNA levels of leptin, adiponectin, interleukin (IL)1β, IL6 and TNFα were measured in visceral adipose tissue.
Results: The results are summarized below. Exposure to neonatal androgens increased circulating levels of leptin and IL1β in young adult females. This was associated with increased mRNA levels of these factors in visceral adipose tissue.There was no change in serum insulin, IL6 or TNFαlevels.

	Male	Female	Androgenized female	ANOVA
Body weight (g)	323.4±6.6	189.6±3.1*	206.3±7.8*,+	p<0.0001
Visceral adipose(g)	1.8±0.2*	1.8±0.2*	2.0±0.3*	p<0.0001
Glycemia (mg/dl)	72.1±1.9	64.3±2.5*	65.7±2.4	p<0.05
Leptin (ng/ml)	1.9±0.1	0.9±0.2*	1.5±0.1*,+	p<0.0001
IL1β(pg/ml)	25.1±3.4	9.1±1.8*	21.5±4.7+	p<0.005
Leptin mRNA	100±18.0	50.4±4.2*	86.6±7.5	p<0.005
IL1β mRNA	100±19.6	85.1±19.6	158.8±32.5	p<0.05
IL6 mRNA	100±19.6	24.8±6.3*	20.8±4.0*	p<0.05
TNFα mRNA	100±17.3	33.3±10.0*	51.6±5.4*	p<0.02

*[Table 1: *different from male, + different from fe]*

Conclusions: Although early exposure to increased androgens may not affect fat mass in young adult females, modifications in its production of cytokines may contribute to pathological processes.

FC15-208 Adipose Tissue

The expression of the adipocyte "insulin sensitivity" cellular markers, protein kinase B (Akt2) and glucose transporter 4 (GLUT4), in relation to adipocyte aquaglyceroporin 7 (AQP7) in childhood obesity

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Background: Childhood obesity predisposes to metabolic disorders. Akt2 influences GLUT4 plasma membrane glucose uptake. Impaired AQP7 regulated, adipocyte glycerol efflux causes adipocyte hypertrophy.
Objective and hypotheses: To study Akt2, GLUT4 & AQP7 protein expression (PE) in lean&obese children in relation to serum insulin & glycerol.
Methods: Primary adipocyte (A) cultures were developed from adipose tissue surgical biopsies of 66 lean (BMI< 85%) & 45 obese (BMI≥95%) prepubertal children (Groups A:2mos-7yrs & B:8-12yrs) & adolescents (Group C:10-15yrs). The PE of Akt2, GLUT4 & AQP7 was studied with Western Immunoblotting and serum fasting insulin and glycerol by ELISA.
Results:
1) *The A of lean showed:*
(a) a significant decrease in Akt2 in the older vs. the younger prepubertal (p=0.01) and pubertal (p=0.01) children,
(b) a significant increase in the 41 and 37KDa AQP7s in the pubertal vs. the prepubertal children of Groups A (p=0.001) & B (p=0.009), respectively.
(2) *The A of obese showed:*
(a) a significant decrease of GLUT4 in the older vs. the younger prepubertal children(p=0.04) and the adolescents (p=0.01),
(b) a significant decrease of GLUT4 in the adolescents vs. their respective lean (p=0.01),
(c) a significant increase of 41KDa AQP7 in the younger prepubertal (Group A) vs. their respective lean (p=0.005).Insulin was significantly increased in the lean & obese children of Groups B & C vs. those in Group A (p≤0.004). Glycerol was significantly increased in the obese children of Group A vs. their lean (p=0.008) & the obese children of Groups B&C(p=0.001).
Conclusions: The decreased GLUT4 & Akt2 in Group B lean together with the increased insulin may reflect the preparation of this age group for the physiological "insulin resistance" of puberty. The obese adolescents with high GLUT4 & low AQP7 PE may have increased glucose uptake but impaired adipocyte glycerol efflux contributing to adipocyte hypertrophy. The increased AQP7 in the lean adolescents possibly reflects the increased energy needs of puberty for glycerol.

FC15-209 Adipose Tissue

Anti-inflammatory SFRP5 and pro-inflammatory WNT5A are abundantly released by adipose tissue and closely related in prepubertal children

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Background: Secreted frizzled-related protein 5 (SFRP5) is an anti-inflammatory adipokine that has been shown to protect against obesity and insulin resistance in mammals. SFRP5 binds to WNT5A to restrain chronic inflammatory states and improve insulin sensitivity.
Objective and hypotheses: We tested in prepubertal children whether SFRP5 and WNT5A are released by adipose tissue and whether adipose tissue and circulating SFRP5 and WNT5A are interrelated.

Methods: We studied the release of these two proteins in adipose tissue obtained from 12 prepubertal children undergoing elective surgery. Circulating SFRP5 was studied in 342 asymptomatic prepubertal children (179 boys and 163 girls) recruited in a primary care setting and circulating WNT5A was also studied in a representative sample of these children (n=210; 115 boys and 95 girls).
Results: SFRP5 and WNT5A were abundantly released by adipose-tissue explants and their releases and serum levels were closely related ($p< 0.001$). Lower levels of circulating SFRP5 were associated with a higher BMI ($p< 0.0001$) and a lower level of circulating HMW adiponectin ($p=0.002$). Higher levels of circulating WNT5A were associated with a more insulin resistant state and with higher transaminase levels, particularly so in children with lower SFRP5 levels (all $p< 0.004$).
Conclusions: This study provides the first evidence that SFRP5 and WNT5A are adipokines that are jointly involved in the metabolism of prepubertal children.

FC16-210 Novel Growth-promoting Treatment

Sodium butyrate helps to rescue the aberrant splicing in the autosomal dominant form of isolated growth hormone deficiency type II

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Background: Isolated GH deficiency type II (IGHD II), the autosomal dominant form of GHD, is primarily a splicing disorder which results from heterozygous splice site mutations that lead to mRNA missplicing and subsequent loss of exon 3 sequences. When misspliced RNA is translated, it produces a toxic 17.5-kDa GH isoform which exhibits a dominant-negative effect on the secretion of 22-kDa isoform.
Objective and hypotheses: Here we test the hypothesis to facilitate the correct splicing of *GH*-1 using Sodium Butyrate (NaB), a short chain fatty acid and histone deacetylase inhibitor.
Methods: Rat pituitary cell line stably expressing hGHRHR (GC-GHRHR) cells were transiently transfected with *wt*-GH or with different GH-splice site mutants, stimulated with GHRH (10nM) and/or treated with NaB (5mM). 24h after treatment: extracellular GH secretion was measured in aliquots of cultured medium by DSL-GH ELISA and the 17.5-kDa vs 22-kDa transcript ratio was determined by qRT-PCR. Further, the differences in the splicing pattern of *wt*-GH vs GH-splice site mutants and the expression of several serine/arginine (SR)-rich proteins and SR-like splicing factors were assessed by Western blot. Dual-luciferase reporter assay was perfomed to test *GH*-1 promoter activation by NaB.
Results: NaB treatment up-regulates *GH*-1 expression, facilitates its correct splicing, increases the amount of 22-kDa relative to the 17.5-kDa isoform, enhances basal and regulated extracellular GH secretion and activates the expression of SR and SR-like splicing factors which specifically promotes the inclusion of exon 3. Further the action NaB by itself, does not activate GHRHR, indicating that its action is mediated by a signalling pathway different from that of GHRHR.
Conclusions: Our findings open the perspectives to treat IGHD II by elevating the GH-*1* transcription level and restoring its correct splicing.

FC16-211 Novel Growth-promoting Treatment

Effect of genetic background and latitude of study site on growth response to recombinant human growth hormone (r-hGH) in patients with GH deficiency (GHD): a post-hoc analysis of PREDICT

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Background: Growth rate tends to be greater in children living at higher latitudes although the underlying mechanisms are unclear.
Objective and hypotheses: Using data from the PREDICT study, we compared height velocity in response to r-hGH therapy in children with GHD living at different latitudes.
Methods: Pre-pubertal children with GHD (n=118) were enrolled from the PREDICT long-term follow-up prospective study (NCT00699855). Data were submitted from 28 centres in 14 countries. Ethnicity background was consistent with country of origin. Absolute latitude was assumed to be that of the study site, with patients categorized into 3 groups: high (>75th percentile: ≥45º), intermediate (25th-75th percentiles: 35º-45º) and low (< 25th percentile: ≤35º) latitudes. The 1-year (Y1) growth response (cm/yr) was assessed & analysed by latitude group and carriage/non-carriage of 5 single nucleotide polymorphisms (SNPs) previously associated with high growth response, within *GRB10*, *IGFBP3* and *CYP19A1*. The effect of latitude and SNP was assessed using a generalized linear model corrected for multiple variables: gender, baseline age and BMI, target height, GH peak and r-hGH dose. In order to look at mechanisms related to latitude effect, the average number of daylight hours during summer at each centre was recorded.
Results: Patients with GHD from high latitudes had a better Y1 growth response than those from intermediate and low latitudes (median [Q1,Q3]: 9.8 [8.5,11.4] vs 8.0 [7.0,9.7] and 8.0 [7.0,10.5] cm/yr, respectively; $P=0.015$). Latitude correlated with summer daylight exposure ($r=0.877$, $P< 0.0001$). In the linear model, growth in Y1 of therapy was significantly affected by an interaction between carriage of a high growth response SNP and latitude ($P< 0.01$ for each gene).
Conclusions: Growth response to r-hGH treatment in GHD may be influenced by both the carriage of specific growth-related SNPs and geographical location, which may be explained by daylight exposure.

FC16-212 Novel Growth-promoting Treatment

Pubertal height gain and adult height in growth hormone treated short children born small for gestational age

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Background: Growth hormone (GH) treatment is effective in improving height in short children born small for gestational age (SGA). During puberty there is often a decline in height SDS resulting in a lower adult height SDS then previously expected.
Objective: To investigate the efficacy of GH treatment (1 mg/m^2/day) in short SGA children and to assess growth during puberty.
Population and methods: In this longitudinal, randomized GH trial, 170 children (83 boys) were included. Age at start of GH treatment was < 8 yr in 109 children (group 1, mean (SD) age 5.8 (1.4) yr), and ≥ 8 yr in 61 children (group 2, mean age 10.1 (1.2) yr). Adult height (AH) and pubertal height gain were analyzed.
Results: AH was reached in 136 children (66 boys). Pubertal height gain for boys and girls in both groups was similar, 25.1 (4.6) vs. 27.4 (4.4) cm (P=0.07) and 15.3 (4.5) vs. 18.3 (3.4) cm (P=0.07), respectively. In boys in group 1, mean height improved from -3.0 at start to -1.6 SDS at AH, and in

group 2 height improved from -2.9 to -2.0 SDS. TH-corrected AH in both groups was -1.1 SDS. In girls in group 1, mean height improved from -3.0 to -1.7 SDS at AH (TH-corrected AH -1.2 SDS). In group 2, height improved from -2.9 to -2.1 SDS (TH-corrected AH -1.5 SDS). In boys and girls in group 1, height SDS at onset of puberty was significantly higher compared to AH SDS (P< 0.001). In boys and girls in group 2, height SDS at puberty was comparable to AH SDS (P= 0.39 and P=0.10, respectively).
Conclusion: GH treatment significantly improves AH in short SGA children, also when children are ≥ 8 years at start of treatment. Pubertal height gain for boys and girls is similar, regardless of age at start of GH treatment.

FC16-213 Novel Growth-promoting Treatment

Intranasal administration of human growth hormone (CP024) results in a linear dose response relationship with Cmax and AUC increasing with dose

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Background: Non-adherence to hGH therapy is estimated to be as high as 66% with 70% of children and carers do not like having to inject themselves on a daily basis. All marketed formulations of human growth hormone (hGH) require subcutaneous injection and CPO24 is a hGH nasal spray containing CriticalSorb™ absorption promoter that offers an attractive non-invasive delivery route. CP024 is a dry powder formulation of hGH and is being developed as a treatment for GH deficiencies in adults and children. The efficacy and IGF-1 response of CP024 is equivalent to a subcutaneous injection.
Objective and hypotheses: To determine the pharmacokinetics (PK) and pharmacodynamics (PD) of intranasal CP024 over a range of doses and develop a PK/PD model.
Methods: A single centre open label three way cross over study was carried out in 7 healthy volunteers to assess the tolerability, PK and PD (IGF-1 induction) of 6 doses of CP024 with doses ranging from 2 - 6 mg delivered using an Aptar Pharma UDS Powder device compared to a subcutaneous injection of Omnitrope. Endogenous hGH was suppressed using a continuous infusion of octreotide.
Results: The results showed that CP024 was well tolerated and the few adverse events observed were mild and transient. CP024 pharmacokinetics were highly reproducible and importantly a linear dose response with Cmax and AUC increasing in line with dose. The 0-2 hour bioavailability was approximately 16%, however, powder was observed outside of the nostrils on dosing and is therefore likely to be an underestimate of the true bioavailability.
Conclusions: CP024 enables the non-invasive delivery of hGH via the nasal cavity. The pharmacokinetics are linear with dose which will allow the accurate titration of dose and therefore the IGF-1 response. Further device optimisation is required to ensure the full dose is delivered effectively.

FC16-214 Novel Growth-promoting Treatment

A phase 1b/2a study of a new long-acting growth hormone (VRS-317) in pre-pubertal children with growth hormone deficiency (GHD)

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Background: VRS-317 is a novel fusion protein consisting of rhGH and two amino acid sequences (XTEN). In GHD adults, single SC doses of VRS-317 were safe, well tolerated and increased IGF-I levels in a dose-dependent manner. At the 0.80 mg/kg dose, the mean t1/2 of VRS-317 was 131 hours. Mean IGF-I SDS was maintained above -1.5 for three weeks.
Objective and hypotheses: Determine the safety, PK, and IGF-I responses to VRS-317 (Phase 1b) and 6 month height velocity (Phase 2a) using VRS-317 dosing regimens that normalize IGF-I in prepubertal children with GHD.
Methods: GHD was documented by auxologic criteria and GH stimulation tests. Subjects were naïve to rhGH with mean age 7.1 y (range 3.8 to 10.9 y). In Phase 1b, following a single VRS-317 dose of 0.80, 1.2, 1.8 or 2.7 mg/kg patients received PK/PD and safety assessments for 60 days. Safety data from a minimum of 8 patients at each dose level are reviewed before each dose escalation. In Phase 2a, patients will be randomized into two groups and treated for 6 months with dose regimens selected from Phase 1b.
Results: The first 8 days treatment data with 0.8 and 1.2 mg/kg VRS-317 are available. A dose response in IGF-I SDS is indicated by greater mean IGF-I changes at 1.2 mg/kg. At 1.2 mg/kg, the mean increase over baseline in IGF-I SDS in all subjects was 1.44 (0.97- 1.83) and persisted for at least 8 days without IGF-I SDS exceeding 2.0. To date, doses have been well tolerated and no unexpected adverse events have occurred enabling further dose escalation.
Conclusions: The preliminary data from GHD children demonstrate that a single SC dose of VRS-317 increases IGF-I levels in a dose-dependent manner for a minimum of 8 days and is well tolerated. Completion of Phase 1b and dose selection for Phase 2a are anticipated by summer of 2013. The completed results of the Phase 1b and doses selected for Phase 2a will be presented.

FC16-215 Novel Growth-promoting Treatment

Analytical and bioanalytical characterization of MOD-4023, a long-acting growth hormone

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Background: Prolor Biotech is a clinical stage public company developing long acting therapeutic proteins utilizing CTP technology. The technology involves fusion of the C terminus peptide of hCG, which is O-glycosylated peptide, to target protein. In order to extend hGH half-life, CTP was directly attached to hGH sequence by means of molecular biology thus enabling the production of a long-acting hGH (MOD-4023). Analytical and bioanalytical characteristics were assessed as part of preparations for pediatric Phase II.
Aims: To characterize MOD-4023 with respect to the protein quality attributes and consistency between manufacturing batches.
Methods: Characterization including physicochemical properties of MOD-4023 was assessed by applying various analytical methods such as viscosity measurements, Capillary Zone Electrophoresis (CZE), Peptide Mapping and Glycosylation Profiling. Cell based activity test utilizing stable hGH receptor expressing cells and measurement of the binding affinity to the receptor was assessed by BIAcore.
Results: MOD-4023 has a low viscosity with comparable syringeability to hGH. Characterization methods showed consistency between clinical batches. Glycoprofyling analysis indicated that the major O-glycan structure in MOD-4023 is mono-sialylated core 1 which is consistent between different batches. MOD-4023 hydrodynamic volume was significantly increased as compared to rhGH. MOD-4023 was shown to bind and activate the human GHR as reflected by cell proliferation and STAT5b phosphorylation.
Conclusion: The high levels of glycosylation contributes to the increase in hydrodynamic volume, resulting in significant elongated circulating time of MOD-4023. MOD-4023 can be manufactured reproducibly while maintaining the protein main characteristics.
With respect to treatment of pediatric patients, MOD-4023 provides once weekly dosing regimen, combined with the benefit of using a 31G needle and overall improved treatment compliance and quality of life.

FC17-216 Obesity

Study of circulating microRNAs in prepubertal obesity

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Background: Circulating microRNAs (miRNAs) are valuable biomarkers and potential therapeutic targets for metabolic diseases.
Objective/hypothesis: In this study, we sought to define the circulating pattern of miRNAs in prepubertal obesity, identifying the miRNAs with the highest prediction power of overweight.
Methods: The genome wide circulating profile of 754 miRNAs was assessed in 10 children (5 lean and 5 obese children, age ~9.3 years). The most relevant miRNAs were cross-sectionally validated in 125 children (age ~9.0 years, 85 lean and 40 obese; BMI z-score -0.3±0.5 and 2.8±0.5, respectively) and prospectively studied in 45 lean children who either increased or decreased their weight between age ~6 and age ~10 years.
Results: The validation study disclosed that 15 specific circulating miRNAs were significantly deregulated in prepubertal obesity, including the decreased miR-221 and miR-28-3p, and increased miR-486-5p, miR-486-3p, miR-142-3p, miR-130b, and miR-423-5p (all $p < 0.0001$) The circulating concentration of these miRNAs was significantly associated with body mass index, waist circumference, percent fat mass, regional fat distribution, and with laboratory parameters such as HOMA-IR, high-molecular-weight adiponectin, C-reactive protein, and lipids. Longitudinally, plasma concentrations of 10 of these circulating miRNAs changed significantly and differently during the 3-year follow-up of children who either increased or decreased their weight. *In silico* analyses showed that the predicted targets of these miRNAs were: FOS, a well-known key-component in stress response; FoxO1, which is a negative regulator of insulin sensitivity and the inositol ITP-kinase B, which is expressed in immune cells.
Conclusion: This study provides the first evidence that circulating miRNAs are deregulated in obese children. The very early detection of an abnormal circulating miRNA profile may be a promising strategy in predicting obesity and its metabolic disturbances in children.

FC17-217 Obesity

POMC DNA hypermethylation variant in obese children and obese adults

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Background: POMC is embedded in the leptin-melanocortin signalling cascade and plays a central role in the regulation of body weight within the hypothalamus. Although gene mutations are rare, twin studies reveal a broad genetic background of body weight. In previous studies we have observed a significant *POMC* DNA hypermethylation variant at the 3'CpG island in peripheral blood cells of obese children, which was present before the onset of obesity.
Objective and hypotheses: To expand our studies and to estimate the heritability of this variant, we have analysed the DNA methylation in an adult cohort (95 normal weight/ 98 obese patients), in trio families with one obese child (n=50) and monozygotic twin pairs (MZ twins)(n=20).
Methods: The DNA methylation was analysed in DNA extracted from peripheral blood cells with a sodium-bisulfite based protocol.
Results: We observed a *POMC* hypermethylation at the 3'CpG island in obese adults compared to normal weight individuals. However the analysis in trio families shows no hints for a classical inherited epigenetic variant. To estimate the degree of genetic determination we analysed obese MZ twins. The MZ twins were not identical methylated at this site, whereas in the majority (60%) the twin with the increased *POMC* methylation weighed more than his sibling.
Conclusions: We were able to reproduce the observation of a *POMC* DNA hypermethylation at the 3'CpG island in an adult cohort. Moreover analysis in trio families reveals a non-heritability pattern of this *POMC* hypermethylation variant. Based on this data we presume, that this hypermethylation occurs based on stochastic events in early embryonic development, which thereby leads to an increased individual risk for the development of obesity later in life.

FC17-218 Obesity

Identification of copy number variants associated with severe early-onset obesity

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Background: Early-onset obesity (EOO), currently affecting 27.6% of Spanish children, predisposes to obesity and related diseases during adulthood. It is considered a multifactorial disorder with high heritability (50-75%). Rare monogenic causes of non-syndromic obesity account < 5% of cases. Genome wide association and genomic studies have identified several genes and regions of susceptibility to obesity, including copy number variants (CNVs) such as deletions at 16p11.2 and a common duplication at 10q26.6 containing the *CYP2E1* gene.
Objective and hypotheses: We aimed to determine the frequency of genomic abnormalities in children with severe EOB.
Methods: Molecular karyotyping (Omni1-Quad and Omni Express SNPa, Illumina) to study 172 patients with EOB and 168 controls. Alterations >100kb including genes and present in less than 1/2000 controls were defined as rare CNVs and validated in probands and parental samples.
Results: At least one rare CNV was found in 23.8% of obese patients versus 17.9% of controls, while two rare CNVs were present in 4.1% patients and 1.2% controls. Duplication at 10q26.6 was found in 7% of cases. All alterations were inherited in patients and co-segregated with the phenotype in several families. Analysis of the genes included in obesity-related CNVs revealed enrichment of pathways related to RNA-polymerase III, mRNA processing and transcription. Among the possible pathogenic variants a duplication of the *NPY gene* was identified in a familiar case with morbid obesity and attention deficit hyperactivity disorder. Two different CNVs were found in more than one patient: 7p22.1 duplications (*RNF216* and *ZNF815* genes) and 9q34.1 duplications (*C9orf62* gene).
Conclusions: Our data reveal a higher burden of rare CNVs in early-onset obese patients compared to controls, including novel CNVs likely associated with familial obesity. Dosage sensitive genes altered by these CNVs are candidates for contribution to the pathogenesis of morbid obesity.

FC17-219 Obesity

Mutation in an intronic CpG island causes deregulation of *MEST* in a family with severe early-onset obesity

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Introduction: *MEST* or *PEG1* (Mesoderm Specific Transcript or Paternally Expressed Gene) is a tissue-specific imprinted gene preferentially expressed from the paternal allele that encodes a member of the α/β-hydrolase superfamily. Alternatively spliced transcript variants encoding multiple isoforms have been identified. Studies in mice have revealed its role in adipose tissue development and adipocyte size, being up-regulated in diet-induced obesity and in genetically modified obese mice.
Case study: We have identified a mutation in a CpG island (chr7: 130.132.836 C>T) located in the differentially methylated region (DMR) of *MEST* intron 1 in a girl presenting morbid early-onset obesity and in her mother. The mother, two other children and other maternal relatives (pending study) also presented with severe obesity of early-onset. The mutation, not present in the 1000 public genomes or in >200 Spanish controls, inhibits the allele-specific methylation within this DMR. *MEST* transcripts were quantified in adipose tissue mRNA from the affected mother and four unrelated obese subjects, along with lymphoblastoid cell line mRNA from controls. The exon 1a isoform was strongly expressed in adipose tissue, being monoallelic of paternal origin in all informative cases. The exon 1c isoform, strongly expressed in lymphoblasts but weakly in adipose tissue, was preferentially (but not exclusively) expressed from the paternal allele. A higher (two-fold) and biallelic expression of the exon 1c isoform was observed in the proband's mother.
Conclusions: Our data indicate that this family presents a novel monogenic form of obesity caused by an intronic mutation in the *MEST* gene that leads to partial imprinting relaxation and *MEST* overexpression in adipose tissue. *MEST* is therefore also an important candidate for epigenetic deregulation in other more common forms of obesity.

FC17-220 Obesity

Aberrant hepatic microRNA expression in non-alcoholic fatty liver disease

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Background: Nonalcoholic fatty liver disease (NAFLD) is a common chronic liver disease in both children and adults, with a wide spectrum of liver status; however, the exact pathogenesis of NAFLD remains obscure.
Objective and hypotheses: The aims of this study were to explore microRNA (miRNA) expression profiles in the liver of rats with NAFLD, and to assess the effect of proinflammatory factors on miRNA expression.
Method: A rat model of NAFLD was used to study miRNA expression; specifically, Sprague-Dawley rats were fed a high-fat diet (HFD) or a control diet for 4 and 12 weeks. The miRNA expression profile of liver tissue was determined at 12 weeks by deep sequencing. Selected miRNAs of interest were then validated by real-time PCR at both 4 and 12 weeks; furthermore, the expression level of these miRNAs was also assessed in HepG2 cells treated with the proinflammatory factors TNFα (10 ng/ml) and IL-6 (25 ng/ml).
Results: Our results demonstrated that consumption of a HFD for 4 weeks caused a simple steatosis, and at 12 weeks this had progressed to steatohepatitis. After removing the expression of both groups lower than 100, our miRNA deep sequencing analysis identified 44 known miRNAs that were upregulated and nine miRNAs that were downregulated more than 1.5-fold in rats fed a HFD, and also predicted 107 novel miRNAs. Among the known abnormal expressed miRNAs, miR-200a, miR-200b, miR-200c, miR-146a, miR-146b and miR-152 were upregulated, the same as what had been found in deep sequencing in both models. Interestingly, the same six miRNAs were increased in HepG2 cells treated with TNFα and IL-6.
Conclusions: Taken together, these findings suggest a critical role for miRNAs in the pathogenesis of NAFLD, and indicate that proinflammatory factors may stimulate aberrant miRNA expression.

FC17-221 Obesity

Hypothalamic suppressor of cytokine signaling (SOCS)3 decreases drastically during development in both normal and overweight rats

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Background: SOCS3 is involved in the development of central leptin resistance by inhibiting the JAK2-STAT3 signaling pathway. However, its role in central leptin sensitivity in overweight subjects throughout development and its involvement in pubertal onset has not been fully elucidated.
Objective and hypotheses: Our objective was to evaluate hypothalamic SOCS3 and phosphorylated (p)STAT3 levels pre- and post-pubertally in order to test our hypothesis that central leptin sensitivity changes differently throughout early development in normal and overweight rats.
Methods: At birth, Wistar rats were organized into litters of 4 (L4; neonatal over-nutrition/overweight) or 12 (L12; control) pups per dam, with equal numbers of each sex in each litter. Rats were sacrificed at postnatal days (PND) 10, 21, 30, 50 and 85. Body weight, length, fat mass and serum leptin levels were measured. Hypothalami were collected and SOCS3 and pSTAT3 protein levels analyzed.
Results: Neonatal overnutrition increased body weight, length, fat mass and serum leptin levels during early development in both sexes. In all rats of both sexes SOCS3 levels decreased dramatically ($P < 0.01$) between PND10 and PND85. The early decrease in SOCS3 was associated with a decline in leptin levels and no change in pSTAT3 levels. In contrast, at PNDs 50 and 85 pSTAT3 levels were decreased ($p < 0.05$) compared to younger females, while in males this decrease was found at PND85 ($p < 0.05$). Surprisingly, this decline in hypothalamic STAT3 phosphorylation was associated with decreased hypothalamic SOCS3.
Conclusions: The relationship between hypothalamic STAT3 phosphorylation and its inhibitor SOCS3 differs between pre and post-pubertal rats. Furthermore, being overweight does not change the pronounced decline of SOCS3 throughout development. Whether this striking reduction in this inhibitor of leptin signaling is associated with modifications in early metabolic control and pubertal onset remains to be determined.

FC18-222 Adrenal Disorders

A mutation in thioredoxin reductase 2 *(TXNRD2)* is associated with familial glucocorticoid deficiency (FGD)

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Background: Novel pathogenic mechanisms involving replicative and oxidative stress have recently been described in FGD; including mutations in *NNT*. NNT supplies high concentrations of NADPH needed for glutathione and thioredoxin anti-oxidant systems to detoxify mitochondrial H_2O_2.
Objective: 6 patients, from a consanguineous Kashmiri family, were diagnosed with FGD between 0.1-12 yr of age and were mutation negative for known causes of FGD.
Methods: Whole exome sequencing was performed on 3 patients, and segregation confirmed by Sanger sequencing of all family members. A *TXNRD2* knockdown H295R cell line was created to investigate redox homeostasis by FACS analysis.
Results: A novel homozygous mutation, p.Y447X in *TXNRD2* was identified segregating with disease. TXNRD2 is a mitochondrial selenoprotein, dependent upon a c-terminal selenocysteine to maintain enzyme activity. *TXNRD2* knockout is embryonic lethal in mice due to cardiac malformation and heterozygous mutations in humans have been linked to dilated cardiomyopathy. We find that *TXNRD2* is ubiquitously expressed in human tissues with high mRNA levels in the adrenal cortex. The predicted consequence of the mutation was premature truncation of the protein before the essential selenocysteine residue, however western blotting of patient lysates revealed complete absence of TXNRD2 protein in patients homozygous for the mutation. RT-PCR of *TXNRD2* suggested that this may be due to mRNA nonsense-mediated decay. *TXNRD2*-knockdown in a human adrenocortical cell line leads to increased oxidative stress with pressure on the glutathione system and increased mitochondrial superoxide production.
Conclusions: A delicate balance of mitochondrial redox regulation controls steroidogenesis at the level of the adrenal gland. We report the first mutation in *TXNRD2* associated with a predominantly adrenal phenotype, indicating the importance of the thioredoxin system in maintaining redox homeostasis in the adrenocortical environment.

FC18-223 Adrenal Disorders

A novel point mutation in the ligand-binding domain of the human glucocorticoid receptor (hGR) gene causing primary generalised glucocorticoid resistance

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Background: Primary Generalized Glucocorticoid Resistance or Chrousos syndrome is a rare familial or sporadic disorder characterized by partial end-organ insensitivity to glucocorticoids. The molecular basis of the condition has been ascribed to inactivating mutations in the hGR gene. We have previously reported a novel heterozygous mutation of the hGR gene in a patient with the condition, which resulted in histidine (H) to arginine (R) substitution at amino acid position 726 in the ligand-binding domain of the receptor.
Objective and hypotheses: To investigate the molecular mechanisms through which the mutant receptor hGRαH726R impairs glucocorticoid signal transduction.
Methods and results: In transient transfection assays, the mutant receptor hGRαH726R demonstrated reduced ability to transactivate the glucocorticoid-inducible MMTV promoter in response to increasing concentrations of dexamethasone and did not exert a dominant negative effect upon the wild-type receptor (hGRαWT). Western Blot analysis revealed equal protein expression of hGRαWT and hGRαH726R. In dexamethasone-binding assays, the hGRαH726R showed a 2-fold decrease in its affinity for the ligand compared with the hGRαWT (20.7 ± 3.25 nM vs. 9.2 ± 3.82 nM). Subcellular localization and nuclear translocation studies confirmed predominantly cytoplasmic localization of both hGRαH726R and hGRαWT in the absence of ligand; exposure to dexamethasone induced a slower translocation of hGRαH726R (60 min) into the nucleus compared with the hGRαWT (15 min).
Conclusions: The mutant receptor hGRαH726R affects multiple functions of hGRα, which alter tissue sensitivity to glucocorticoids.

FC18-224 Adrenal Disorders

Digenic inheritance of mutations in antioxidant pathway genes in a patient with familial glucocorticoid deficiency (FGD)?

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Background: Mutations in the antioxidant genes nicotinamide nucleotide transhydrogenase (*NNT*) and thioredoxin reductase 2 (*TXNRD2*) have been associated with FGD. NNT generates high concentrations of NADPH for ROS detoxification by the glutathione and thioredoxin antioxidant systems. In a male patient we previously identified a homozygous mutation in glutathione peroxidase 1 (*GPX1*). The mutation was heterozygous in his parents and absent in an unaffected sibling.
Methods: A *GPX1*-knockdown H295R cell line was created and its cell viability and levels of apoptosis were compared to a scrambled control. Wt vs. *Gpx1*$^{-/-}$ mouse adrenals were analysed. Whole exome sequencing was employed to identify other candidate gene(s).
Results: KD-GPX1 cells had 50% less basal GPX activity and were less viable than scrambled when exposed to oxidative stress. Adrenals from *Gpx1*$^{-/-}$ mice showed no gross morphological changes and corticosterone levels were not significantly different from their wild-type counterparts (in contrast to the *Nnt* mutants). Sequencing of >100 FGD patients did not reveal any other *GPX1* mutations. Taking this equivocal data together we hypothesized that there could be a second gene defect present in this proband. Whole exome sequencing revealed a homozygous loss-of-function mutation in peroxiredoxin 3 *PRDX3* (p.Q67X) in this patient, his parents were heterozygous but his unaffected brother was homozygous.
Conclusions: GPXs and PRDXs work simultaneously to reduce H_2O_2, preventing cellular damage. The adrenal cortex has a particularly harsh oxidative environment due to the p450 steroidogenic enzymes, potentially increasing its sensitivity to redox changes. Previous studies have implicated GPX1 and PRDX3 as regulators of steroidogenesis by modulation of ROS levels. Our data show that loss of *PRDX3* alone is insufficient to cause adrenal failure and suggest that mutation in *GPX1* either alone, or in combination with *PRDX3* mutation, may tip the redox balance and cause FGD.

FC18-225 Adrenal Disorders

Utility of whole-exome sequencing in the diagnosis of adrenal insufficiency

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Background: In recent years a growing number of causative gene mutations have been identified which cause a myriad of syndromes having adrenal insufficiency as one of their main characteristics. The evolution of adrenal insufficiency is dependent on the variant and the particular gene affected. Common practice is for candidate genes to be sequenced individually, which is time consuming and complicated by overlapping clinical phenotypes between syndromes leading to negative results. The increasing availability and cost effectiveness of whole-exome sequencing (WES) is proving to be a powerful alternative. WES as a diagnostic tool offers rapid accurate screening for disease variants, thus reducing erroneous clinical diagnoses and enabling tar-

geted treatment plans that should result in better long-term clinical outcomes.
Methods: WES was performed on 38 probands referred to our unit with a clinical diagnosis of familial glucocorticoid deficiency. All had been screened for mutations in *MC2R*, *MRAP* and *STAR* and most for mutations in *GPX1* and *NNT*.
Results: We made a genetic diagnosis in 10 probands plus two of their affected siblings, identifying mutations in the following genes; *NR0B1* in 3 patients, *CYP11A1* in 2 patients, *AAAS* in 2 patients, *MC2R* in 1 patient, *NNT* in a pair of siblings and *AIRE* in two siblings. Most mutations were novel changes, which were confirmed by direct Sanger sequencing of the index case and other affected family members.
Conclusions: A genetic diagnosis was therefore readily achieved in 25% of patients that underwent WES. It is feasible that many other cases are caused by novel genes. We believe that the evolution of WES into a diagnostic tool offers a rapid cost effective way of screening patients for monogenic diseases. It offers particular use in adrenal conditions in childhood due to the large number of genes needing to be sequenced to gain a definitive diagnosis.

FC18-226 Adrenal Disorders

A 13-year-old girl with aldosterone-producing adenoma having a somatic mutation of *KCNJ5*

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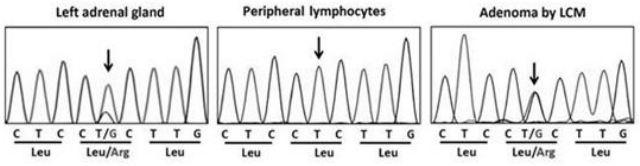
Background: Aldosterone-producing adenoma (APA) is one of common subtypes of primary aldosteronism. Somatic mutations of *KCNJ5* were recently identified in about 40% of APA in adults, while not in children.
Case report: A 13-year-old girl suffered from recurrent headache and nausea for two years. On examination, her blood pressure was 149/105 mmHg. Laboratory data showed hypokalemia (serum K 2.7 mEq/L) and normal serum aldosterone level (286 pg/mL) with suppressed plasma active renin concentration (< 2.0 pg/mL). Imagings of adrenal gland were not informative. By selective adrenal venous sampling, aldosterone levels in the right and left adrenal veins were 5030 and 36300 pg/mL after stimulation with 250 μg of ACTH, respectively. The rations of aldosterone (pg/mL)/ cortisol (μg/dL) were 22 and 151, respectively. She was diagnosed as having APA in the left adrenal gland. The left adrenal gland was resected laparoscopically. Macroscopic examination showed the presence of a well circumscribed tumor measuring 20x15x8 mm in the left adrenal gland. Pathological diagnosis was the adrenocortical adenoma.
Method: We extracted genomic DNA from the left adrenal gland and peripheral lymphocytes, and analyzed *KCNJ5* by PCR-based sequencing. We also dissected out the adrenocortical adenoma by laser-capture microdissection (LCM) and verified the detected mutation of *KCNJ5* in genomic DNA of the adenoma.
Result: We identified a mutation (p.Leu168Arg) in DNA of the left adrenal gland. The mutation is one of the recurrent somatic mutations found in APA, which causes loss of Kir3.4 channel selectivity and a positive shift in the reversal potential. The mutation was absent in her peripheral lymphocytes and was detected as a heterozygote in the adenoma by LCM, indicating a somatic mutation.
Discussion and conclusion: This is the first child case with APA proven to have a somatic mutation of *KCNJ5*. Somatic *KCNJ5* mutation can cause APA in children as well as adults.



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FC18-227 Adrenal Disorders

Are female paediatricians more stress resistant than their male colleagues? A study on the endocrine impact of 24h-shifts in physicians based on urinary steroid metabolomics

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Background: Being a physician is accompanied by emotional and physical stress. Especially working 24h shifts are mentioned to be a major stressor.
Objective and hypotheses: Our study aimed to investigate the effect of 24h-shifts on the steroid metabolome.
Methods: 22 paediatricians (10♀ , 12♂) aged 27 to 41 yrs collected two 24h urine samples: one during a 24h-shift at the children's hospital Giessen (on-duty) and one on a free weekend (off-duty). The urine samples were analyzed by gas chromatography-mass spectrometry. The sum of daily urinary excretion rates per m^2 body surface for cortisol, tetrahydrocortisol, 5α-tetrahydrocortisol, tetrahydrocortisone, α-cortol, β-cortol, α-cortolone and β-cortolone represented the cortisol metabolites (CM).
Results: Doctors on duty had a median [25-75.percentile] of CM of 8242 [4796 -10821] μg/d/m^2, whereas the median off duty was 5859 [4329-8079] μg/d/m^2, differing significantly (p=.0037). No significant difference for the CM on duty could be detected if sorted by age (≤30 vs. >30 yrs), hours of sleep (< 4 vs. ≥4h), number of sleep disturbances (< 3 vs. ≥3) or experience (≤ 5 vs. >5yrs of training). The excretion rate of CM was lower in females on duty (median 5066 [3459 -8056] μg/d/m^2) as well as off duty (median 4285 [3872-5347] μg/d/m^2) compared to males on duty (median 10909 [9711-12835] μg/d/m^2) and off duty (median 7195 [5711-8523] μg/d/m^2), showing highly significant differences (p=.0001/ p=.0034 respectively). Subtracting the excretion rates of CM off duty from those on duty, female physicians had significant lower differences in comparison with their male colleagues (p=.0071).
Conclusions: Physicians working 24h shifts experience enormous adrenocortical stimulation. Female physicians react differently from males to the stimulus of 24-hour shifts. This could indicate a higher stress resistance of females compared to males. Further studies with the long-term goal of optimising working conditions for physicians are needed.

FC19-228 Thyroid

Novel mutations in the carboxy-terminal region of DEHAL1 and iodotyrosine dehalogenase deficiency

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Introduction: DEHAL1 is the enzyme that recycles iodide in the thyroid gland through deiodination of mono- and di-iodotyrosines (MIT, DIT), releasing iodide for sustained synthesis of thyroid hormone. Only four different *DEHAL1* mutations are known to date in patients from consanguineous families with hypothyroidism, goiter and variable mental retardation.
Objetives: Clinical and molecular characterization of *DEHAL1* gene in families with hypothyroidism and suspected iodotyrosine deiodinase deficiency.
Methods: Direct sequencing of *DEHAL1* coding region in 26 individuals from 6 families with positive *in vivo* ^{131}I- labeled iodotyrosine deiodination test, as performed in the 1980s, or negative perchlorate or thiocyanate discharge tests. Urine MIT/DIT was quantified by HPLC-MS/MS. Pathogenicity of mutations was analysed *in silico* by 5 functional prediction programs.
Results: Three families were consanguineous. Two index cases (ICs) were hypothyroid during childhood, but euthyroid as adults consuming iodized table salt, while the rest require LT4 treatment. Four individuals in two pedi-

grees underwent thyroidectomy for compressive goiter.
We identified 4 (damaging) novel mutations segregating in 4 different families (p.K258N, p.E271LK, p.V265M, p.R279S) and a putative SNP (p.R246Q). All mutations are localized in the carboxy-terminal region of DEHAL1 and harboring a FMN-binding site. No changes were found in one family.
All patients tested (12/26) had elevated MIT (251-1444 nmol/L; N< 5.2 nmol/L) and DIT (18.4-66 nmol/L; N< 0.8 nmol/L), excepting for one of the patients currently under LT4 treatment.
Conclusions: Novel DEHAL1 mutations suggest a relevant role of the carboxy-terminal tail and that all FMN-interacting regions are important to achieve full reductive potential of the enzyme. Absence of mutations in pedigrees with typical features of dehalogenase deficiency suggests elusive gene defects or the existence of yet unidentified DEHAL1 partner proteins.

FC19-229 Thyroid

Monoallelic mutations in *TSHR* and *DUOX2* do not act as single Mendelian factors but as risk factors for congenital hypothyroidism: pathway burden hypothesis

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Background: Biallelic mutations in the *TSHR* or the *DUOX2* cause congenital hypothyroidism (CH). However, some CH patients have only monoalellic mutation. Considering high frequencies of monoallelic mutation carriers in general Japanese population (*TSHR* 1/172, *DUOX2* 1/67), a minor fraction of carriers is thought to develop CH. In this study, we hypothesized that monoallelic mutations act as risk factors for developing CH.
Subjects and methods: We enrolled 401 Japanese patients with primary CH that were identified in the frame of newborn screening for CH. *TSHR* was sequenced in all subjects. Identified monoallelic *TSHR* mutation carriers were further sequenced for *DUOX2*. We compared the frequencies of *TSHR* heterozygote and *TSHR/DUOX2* double heterozygotes between the patient cohort and general population. The risk for CH was calculated based on two by two tables. Probabilities of CH affection among monoallelic mutation carriers were estimated by a Bayesian method.
Results: We identified 27 *TSHR* heterozygotes, including four *TSHR/DUOX2* double heterozygotes. [genotype (*TSHR*/*DUOX2)*: R450H/E327X, R450H/K530X (N=2), R450H/V779M]. The frequencies of *TSHR* heterozygote was 6.7% (27/401) and 0.58% (1/172) in the patient cohort and general population, respectively, and odds ratio (OR) for developing CH was 12.3. Correspondingly, the frequencies of *TSHR/DUOX2* double heterozygotes were 1.0% (4/401) and 0.0087% (1/172×1/67) in the patient cohort and general population, respectively, and OR was 116.1. The estimated probability of CH affection was 0.38% among *TSHR* heterozygotes, and was 3.7% in *TSHR/DUOX2* double heterozygotes.
Conclusions: Our data indicate that monoallelic mutations in *TSHR* and *DUOX2* do not act as single Mendelian factors but as extremely strong risk factors for CH. Accumulation of "subtle" burdens in the thyroid hormone-producing pathway (*e.g.*, heterozygous mutations) are required to develop CH, whereas one "large" burden (*e.g.*, biallelic mutations) can cause CH.

FC19-230 Thyroid

Dyrk1A (Dual-specificity tyrosine (Y)-phosphorylation regulated kinase 1A) overexpression is linked to congenital hypothyroidism in Down syndrome

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Background: Down Syndrome (DS) patients have a predisposition for Congenital Hypothyroidism which may aggravate their mental status.
Hypothesis: The three copies of *Dyrk1a* gene, localized in chromosome 21, may cause the thyroidal dysgenesis in DS.
Objective: Understand the molecular mechanisms underlying this hypothesis.
Methods: The transgenic Dyrk1a (TgDyrk1a) mouse has three copies of the Dyrk1a gene and was obtained by Bacterial Artificial Chromosome engineering (mBACtgDyrk1a). We compared T4 and TSH plasmatic levels of 8-12 weeks old (early ages) TgDyrk1a and wild type (wt) mice and analyzed their thyroid structure in histological sections. Embryonic thyroid development from E13.5 to E17.5 was analysed by immunofluorescence with anti-Nkx2.1 and anti-T4 antibodies, markers of early thyroid development and final differentiation respectively. In parallel, the expression of transcription factors Nkx2-1 and FoxE1 involved in thyroidogenesis, and thyroglobulin were studied by qRT-PCR at the same embryonic stages.
Results: TgDyrk1a young adult mice have a significant lower plasmatic T4 level (2.4 ng/mL versus wt: 3.7 ng/mL; p = 0.019) and an increased plasmatic TSH level (114mUI/L versus wt: 73mUI/L). Their thyroidal follicles surface is larger (6955µm² versus wt: 5755µm²). At E15.5 the primary TgDyrk1A thyroids are double in size comparing to wt (p= 0.01) but their differentiated follicular surface is two times smaller at E17.5 (p= 0.01). We also observed a significant increase of RNA levels of Nkx2-1 (p=0.009), Foxe1 (p=0.025) at E13.5, and Thyroglobulin (p=0.04) at E17.5.
Conclusions: TgDyrk1a mice have abnormal thyroid development with ultimately mild hypothyroidism. An increase of the transcription factors expression and their target genes involved in thyroid development and function was documented. The young adult thyroids phenotype is probably due to a compensation mechanism. We are studying candidate genes as Dyrk1a targets using thyroidal cell lines.

FC19-231 Thyroid

Permanent congenital hypothyroidism due to a novel heterozygous mutation in the promoter region of the PAX8 gene in a girl with Down syndrome

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Introduction: Thyroid dysfunction is common in newborn infants with Down syndrome (DS) but defects in organogenesis have not been described.
Case study: A female infant, BW 2.83 kg & gestation 39 weeks had trisomy 21 complicated by atrio-ventricular septal defect and patent ductus. Newborn screening showed capillary TSH 43.8 mU/L(day 5), venous TSH >150 mU/l and free T4 15.1 pmol/L (day 12), thyroid peroxidase (TPO) antibodies 409 IU/ml (normal < 50 IU/ml) and thyroglobulin 103 ng/ml (normal < 55 ng/ml). Thyroid ultrasound showed a small gland (vol 0.76 ml [ref range 1.0-3.3]) with heterogenous echotexture and cystic changes. Scintigraphy showed

normal uptake into a eutopic gland. The infant was treated with thyroxine and underwent cardiac repair at 69 days. Sequencing analysis of candidate genes involved in thyroid gland development revealed a new heterozygous maternally inherited mutation (-3C>T) close to the transcription initiation site of the *PAX8* gene. Electromobility shift assay (EMSA) studies of the WT and the mutant *PAX8* sequence incubated with nuclear extracts from PCCL3 cells exhibited that the sequence at position -3 is not involved in specific protein binding. However, the mutant *PAX8* promoter showed a significantly reduced transcriptional activation of a *luciferase* reporter gene *in vitro* tested in HEK, PCCL3 as well as in HeLa cells indicating that the mutation is very likely to lead to a reduced *PAX8* expression. At 3.8 years the dose of L-thyroxine was reduced from 50 to 25 µg daily after which TSH rose to 53.6 mU/l, with fT4 12.1. Maternal blood showed fT4 12.6 pmol/l, TSH 16.13 mU/l, TPO >1000 IU/ml and the mother commenced thyroxine.

Conclusion: The persistent rather than transient nature of our patient's hypothyroidism is attributable to the PAX8 mutation rather than maternal thyroid antibodies. Further study in infants with DS and TSH elevation is needed to determine whether or not there is a true association between DS and PAX8 mutations.

FC19-232 Thyroid

Dynamics of TSH secretion under TRH stimulation and genetics of central congenital hypothyroidism

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Background: Central Congenital Hypothyroidism (CCH) is under-diagnosed in countries using TSH-based neonatal screening programs for CH. The TRH test can discriminate between hypothalamic or pituitary CCH, but recently its clinical usefulness has been discussed. The genetic basis of CCH is still largely unknown.

Objective and hypotheses: To investigate correlations between the TRH-stimulated dynamics of TSH secretion and the underlying genetics of CCH.

Methods: Etiological investigation and molecular study of 15 CCH patients, following a best candidate gene approach. Long TRH test (180 min) was performed with TSH determinations at 0,15,30,45,60,120,180 min. Magnitude of the response and dynamics of basal TSH recovery were analyzed by peak/0' and 180'/0' ratios, respectively.

Results: Following van Tijn's criteria, 47% (7/15) of cases were hypothalamic, with TSH peaks>25mU/L (mean:59), peak/0' ratio>9 (mean:12) and absence of basal TSH recovery, with 180'/0' ratio>1.6 (mean:1.96).

40% (6/15) of patients had pituitary CCH, showing decreased TSH to TRH response with TSH peaks< 20mU/L (mean:5.3), peak/0' ratio< 6 (mean:4) and complete basal TSH recovery with 180'/0' ratio< 1.6 (mean:1.1). Age at diagnosis of hypothalamic CCH is higher than that of pituitary CCH (9 vs. 5 years), and TSH and FT4 levels are also significantly higher (TSH: 6.15 vs. 0.5mU/L; T4L: 1 vs. 0.6ng/dl). Two patients had "mixed" response, one of them with hypothalamic-pituitary hypoplasia.

Genetic defects were identified in 27% (4/15) of cases (*POU1F1*: p.R265W mutation, *IGSF1*: complete hemizygous deletion, *Prader-Willi S.*: cr. 15q paternal deletion and a suspected *GATA2* (*sGATA2*) defect for associated FSH/LH deficiency.

Conclusions: Pituitary CCH is more severe and is diagnosed earlier than hypothalamic CCH. The 4 pituitary genotypes identified show characteristic TSH secretory profiles (*POU1F1*: flat, *IGSF1* and *Prader-Willi*: quantitatively low but normal dynamics and *sGATA2*: mild quantitative defect).

FC19-233 Thyroid

Factors associated with hearing impairment in young adult patients with congenital hypothyroidism treated since the neonatal period: a national population-based study

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Background: Untreated hypothyroidism is known to impair hearing, but little is known about the long-term hearing of patients treated for congenital hypothyroidism (CH) since the neonatal period.

Objective: To assess hearing and its determinants in a population-based registry of young adult patients with CH.

Patients and methods: In total, 1202 of the 1748 subjects diagnosed with CH in the first 10 years after the introduction of neonatal screening in France completed a questionnaire on health status, including self-declared hearing loss, at a median age of 23.4 years. Audiograms were obtained for one third (37/107) of the patients declaring hearing loss.

Results: These patients had a risk of self-declared hearing loss more than three times higher than that for the reference population [RR = 3.7 (2.9-4.7)]. Hearing impairment was diagnosed at a median age of 7.0 (3.4-19.0) years and 17 % of patients required hearing support. Hearing loss was associated with the type of CH (patients with athyreosis and gland *in situ* being more frequently affected than those with ectopic gland [RR = 2.61 (1.77-3.88)]), -disease severity, as assessed by the bone maturation delay at the time of diagnosis, with at least one knee epiphyseal ossification center absent in the most severe form [RR= 2.29 (1.39-3.79)] and with other associated chronic diseases [RR = 3.64 (2.35-5.62)]. It was also less strongly associated with low serum FT4 levels (< 5.0 pmol/l) at diagnosis [RR = 1.47 (0.96-2.23)]. Hearing loss was mostly bilateral (90%), mild to moderate (96%), of the sensorineural type (76%) and concerned high or very high frequencies.

Conclusions: Despite major improvements in prognosis, hearing loss remains a significant problem, particularly in patients with severe CH. Parents and primary care providers should be aware of this risk, as early diagnosis and intervention could improve the long-term prognosis of these patients.

FC20-1483 Late Breaking Abstracts

Whole exome sequencing identifies FAM111A as a new cause of autosomal recessive Kenny-Caffey syndrome

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Background: Kenny-Caffey syndrome (KCS) is characterized by pre- and post-natal growth retardation, short stature, small hands and feet, microcephaly, hypoparathyroidism, osteosclerosis and recurrent bacterial infections. Most cases of autosomal recessive KCS are due to mutation of the *TBCE* gene, which also causes the related disorder Sanjad-Sakati syndrome.

Objective and hypotheses: To perform whole exome sequence analysis to identify the genetic basis for KCS in a young girl with normal sequences for the *TBCE* gene.

Methods: We extracted genomic DNA from the proband, her parents and three unaffected siblings and performed whole exome sequencing on samples from all subjects. Genomic DNA was extracted from paraffin tissue blocks from her deceased affected sibling. Sequence processing and variant calling were performed using standard bioinformatics tools and an autosomal recessive model. Genotypes were confirmed by Sanger sequencing. Polyphen-2 and I-TASSER were used to predict the effect of missense mutations on protein structure and function.

Results: We studied a young Swiss girl with KCS; an older brother had died as an infant of KCS-related sepsis. There was no parental consainguinity. We identified five candidate genes, but only one, *FAM111A* at 11q12.1, showed

biallic mutations in both the proband and her affected sibling, homozygous c.A1241G that is predicted to replace Tyr at position 414 with Cys (p.Y414C). Both parents and the three unaffected sibs were heterozygous. This non-conservative mutation is predicted to destablize the FAM111A protein leading to loss of function.
Conclusions: Previous studies had identified FAM111A as a host range restriction factor that is specifically targeted by SV40 LT. Although FAM111A is expressed in the parathyroid, it is uncertain how depletion of FAM111A leads to hypoparathyroidism or the other features of KCS. Nevertheless, our studies indicate that loss of FAM111A function is a second genetic cause of AR KSC.

FC20-1484 Late Breaking Abstracts

Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity

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Background: Melanocortin receptor accessory proteins (MRAPs) modulate signaling of melanocortin receptors *in vitro*.
Objective and hypotheses: To investigate the physiological role of brain-expressed Melanocortin 2 Receptor Accessory Protein 2 (MRAP2), we characterized mice with whole body and brain-specific targeted deletion of *Mrap2*, the interaction between Mrap2 and Mc4r, and humans with mutations in *MRAP2*.
Methods: We created mice with knockout (KO) of *Mrap2* in either all tissues (KO mice) or only in brain-specific Sim1 neurons using homologous recombination and Cre-Lox technology. The effect of Mrap2 upon alpha MSH-stimulated Mc4r function was examined in cells transfected with both genes and assessed by cAMP generation. *MRAP2* mutations were identified by DNA sequence analysis in two cohorts of patients with severe, early onset obesity.
Results: Mice with whole body and brain-specific KO of *Mrap2* develop severe obesity at a young age. Older, but not younger, KO mice are hyperphagic. KO mice, even when pair-fed to a normal food intake, develop obesity, indicating a metabolic effect of Mrap2 on energy expenditure. Mrap2 interacts directly with Mc4r, a protein previously implicated in mammalian obesity, and enhances Mc4r-mediated generation of cyclic AMP, suggesting that alterations in Mc4r signaling may be one mechanism underlying the association between *Mrap2* disruption and obesity. In humans with severe, early-onset obesity, we found four rare, potentially pathogenic genetic variants in *MRAP2*, including a stop codon near the beginning of the protein.
Conclusions: Mrap2 is required for normal energy balance in mice and may contribute to body weight regulation in humans.

FC20-1485 Late Breaking Abstracts

Absence of renal resistance to PTH in PDE4D-mutated acrodysostosis patients: regulation of cAMP/PKA pathway by PDE4 may be tissue and agonist-specific - example of renal PTH signaling pathway

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Background: *PRKAR1A* and *PDE4D* mutations causing acrodysostosis and *GNAS* mutations causing pseudohypoparathyroidism 1a are responsible for defect in cAMP-PKA signaling. These disorders present a similar skeletal dysplasia due to PTHrP resistance, but distinct resistance to hormones signaling through cAMP: renal resistance to PTH is present in patients with *PRKAR1A* and *GNAS*, but not *PDE4D* mutations.
We hypothesized that PDE4D may not regulate renal cAMP response to PTH.
Methods: We used the renal HEK293 cells stably expressing PTH1R and PDE4D. We stimulated them by PTH (0,5µg/ml) and PGE2 (1µM) in absence or presence of rolipram (50 µM), a specific PDE4 inhibitor, and measured intracellular cAMP production and PKA activity (cre-luciferase reporter assay).
Results: 1) PGE2 and PTH both increased cAMP levels (baseline: 1,29; +PGE2: 7,82; +PTH: 248,10 fmol/ng of protein; p< 0,0001 and p=0,0002 respectively). Rolipram significantly potentiated stimulation of cAMP production by PGE2 (7,82 vs 176,8; p< 0,0001) but not by PTH (248,10 vs 552,20; p=0,15).
2) Similarly PGE2 and PTH both increased significantly cre-luciferase activity (fold-increase (FI) 54,44 and 92,05 respectively). As observed for cAMP production, rolipram significantly potentiated stimulation of cre-luciferase activity by PGE2 but not by PTH (FI 173,50; p=0,03 vs FI 137,8; p=0,09 respectively; delta FI 3,36 vs 1,57 p< 0,0001).
Conclusions: These results indicate that PDE4D regulates cAMP-PKA signaling by PTH to a lesser extent than that by PGE2. Further studies are required to understand the mechanisms leading to this difference, and determine if it contributes to the absence of renal PTH resistance in patients with PDE4D mutations.

FC20-1486 Late Breaking Abstracts

Sonic Hedgehog pathway involvement in adrenal cortex development and tumorigenesis

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Background: The role of Sonic Hedgehog (SHH) signaling in human adrenal embryogenesis and tumorigenesis is unknown.
Objectives: To analyze the involvement of the SHH pathway in adrenal development and tumorigenesis and the effects of SHH inhibition in adrenocortical tumors (ACT).
Patients/Method: 81 patients with ACT (61 children), 19 control adrenals (10 pediatric) and a panel of 62 paraffinized normal adrenals (43 fetal; 20-37 wks) were analyzed. The expression of SHH pathway genes was evaluated by qPCR and IHC. ACT H295A cells proliferation/viability and adrenal steroids production was analyzed after treatment with SHH antagonist Cyclopamine (2-30mM; 24-96h). Statistics: Mann-Whitney, linear regression, Kaplan-Meier/Log Rank.
Results: SHH pathway is active in fetal and postnatal adrenals. SHH/GLI1 staining was restricted to the subcapsular region; SMO/GLI2/GLI3 were strongly expressed throughout the cortex. SHH, PTCH, SMO, GLI1, GLI2

and GLI3 mRNA was expressed in pediatric and adult normal adrenals, although higher expressed in adult tissues ($p< 0.05$). Childhood ACTs presented lower expression of SHH ($p< 0.01$), PTCH ($p=0.03$), SMO ($p< 0.01$), GLI1 ($p< 0.01$) and GLI3 ($p=0.01$) and higher expression occurred in less aggressive tumors. Conversely, adult ACTs presented higher expression of PTCH ($p=0.03$), SMO ($p=0.04$), GLI3 ($p=0.02$) and SUFU ($p< 0.01$). In vitro inhibition of SHH pathway with 20-30mM of Cyclopamine resulted in decreased cell viability and proliferation ($p=0.02$) and 51% and 63% reduction in cortisol and DHEAS production.
Conclusions: these original data show that SHH pathway is involved in fetal and postnatal adrenal development. Differential expression of this pathway is found in ACTs, being more active in less aggressive pediatric and in adult ACTs. In addition, SHH pathway inhibition impaired cell viability/proliferation as well as cortisol and DHEAS production. SHH pathway is deregulated in ACTs and is a new potential therapy target to be explored.

FC20-1487 Late Breaking Abstracts

Whole exome sequencing and functional studies identify a germline gain-of-function mutation in GNA11 as a novel cause of autosomal dominant hypoparathyroidism

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Background: Most cases of Autosomal Dominant Hypoparathyroidism (ADH) are due to gain-of-function mutations in *CASR* or dominant inhibitor mutations in *GCM2* or *PTH*. We evaluated a family with ADH in which affected subjects had normal sequences in these genes.
Objective and hypotheses: To identify the genetic basis for ADH in a multigenerational family.
Methods: We obtained clinical and biochemical data from five of ten affected subjects and performed whole exome sequence analysis on DNA from two affected sisters and their affected father. Functional studies were performed by expression of wild type and mutant cDNAs in HEK293-CAR cells expressing CASRs.
Results: Bioinformatic filtering of variants implicated in development or function of the parathyroid glands revealed a heterozygous mutation, c.G179T, in exon 2 of *GNA11*, which encodes the α subunit of G11, the heterotrimeric G protein that couples CASR to signal activation in parathyroid cells. Sanger sequencing confirmed the mutation in these as well as two additional affected subjects. The mutation was not present in public or private databases. The mutation is predicted to replace a conserved Arg by Leu at position 60, and to disrupt a salt bridge between Arg60 in the GTPase domain and Asp71 in the helical domain that stabilizes GDP binding, and thereby lead to enhanced release of GDP. In functional studies, Gα11 R60L had leftward shifts in extracellular Ca^{2+} concentration-response curves with significantly decreased mean EC_{50} compared to wild type Gα11 in three assays of CASR-activated phospholipase Cβ: accumulation of intracelluar Ca^{2+}, phosphorylation of ERK1/2, and activation of a SRE-luciferase reporter. In contrast to subjects with *CASR* mutations, affected subjects with *GNA11* mutations lacked hypercalciuria and had normal serum magnesium levels
Conclusions: This gain-of-function germinal mutation in *GNA11* appears to affect CASR signaling in the parathyroid but not kidney, and represents a novel cause of ADH.

FC20-1488 Late Breaking Abstracts

Asfotase alfa improves skeletal mineralization and respiratory function in infants and young children with hypophosphatasia: results from up to 12 months' treatment

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Background: Hypophosphatasia (HPP) is a, life-threatening, rare systemic and bone disease resulting from mutations in the tissue-nonspecific alkaline phosphatase (TNSALP) gene. There is no approved treatment. Perinatal- or infantile-onset HPP is usually fatal due to respiratory insufficiency. Prior data show that asfotase alfa, a recombinant human TNSALP, improved skeletal mineralization and physical function in perinatal or infantile HPP.
Objective: Examine the effects of asfotase alfa in children ≤ 5 y.o. with HPP symptoms at age ≤6 mo.
Methods: Multinational, Phase II, open-label trial of asfotase alfa (SC, 2 mg/kg 3x/wk or 1 mg/kg 6x/wk). The primary endpoint was effect on skeletal manifestations at Wk 24, assessed using a 7-point Radiographic Global Impression of Change (RGI-C) scale (-3: severe worsening; +3: complete healing). Other evaluations included respiratory status and safety.
Results: At this interim analysis, 15 patients (pts) were enrolled, median baseline (BL) age 21 wks (range, birth-304), median treatment duration 72.1 wks (range, 0.4-120.4 11 pts >52 wks). One pt withdrew consent (Day 16) and died from disease-related complications. At Wk 24, median RGI-C was +2 (range: 0.3-3.0; $p=0.001$, $n=13$); at Wk 48, all 10 pts with available data had RGI-C ≥2. At BL, 5 pts (age: birth-15.3 wks) required respiratory support; 2 later no longer required support. Of the 10 pts not requiring respiratory support at BL, the 3 youngest (BL age: 17.0-21.1 wks) later required support; 1 remained on support at last observation (Wk 12). The most common treatment-related AEs were mild or moderate injection site reactions. There were no treatment-related discontinuations, SAEs or deaths.
Conclusions: Asfotase alfa remarkably improved skeletal mineralization, enhanced respiratory function, and was well tolerated in severely-affected infants and young children most of whom were treated for >52 wks. These data further support the promise of asfotase alfa in HPP.

Poster Presentations

P1-d1-234 Adrenals and HPA Axis 1

Clinical features and mutation spectrum of the *StAR* gene of patients with congenital lipoid adrenal hyperplasia

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Background: Congenital lipoid adrenal hyperplasia (CLAH) is caused by mutations in the *StAR* gene and StAR protein plays a critical role for transport of cholesterol to mitochondria.
Objective and hypotheses: This study aimed at investigating *StAR* mutation spectrum and associated clinical and endocrinologic characteristics in CLAH patients.
Methods: The study included 33 unrelated families with CLAH diagnosed by endocrine profile and mutation analysis. Clinical features, endocrine data, and radiologic finding were reviewed retrospectively. Seven exons and associated intronic flanking regions of the *StAR* gene were amplified by PCR and directly sequenced.
Results: All patients presented with severe adrenal insufficiency and salt wasting. Current age of the subjects ranged from 11 months to 18 years. Sixteen patients were 46,XY karyotype and 13 had a 46,XX. One patient with 46,XY, p.Q258X/ p.R272H of the *StAR* gene, was incompletely virilized and raised as a boy. Two patients with 46,XX experienced onset of spontaneous puberty. Basal ACTH and renin levels were extremely elevated, whereas most adrenal and gonadal steroids decreased in all patients. The genotype of the *StAR* was clarified in all the patients, identifying 8 different mutations. Of these, p.Q258X was the most common (87.9%, 57/66 alleles). The A218V mutation was identified in two of the 66 alleles (3%). The other mutations were p.R182H, p.R182C, c.745-6_810del, p.V187M, p.K98R, and p.R272H. And each of them was detected one of the 66 alleles (1.5%). The novel p.K98R and p.R272H variants were not found in 1000genomes database, making these variants unique to our CLAH patients.
Conclusions: Mutation analysis of *StAR* reveled that p.Q258X is the most common, suggesting the founder effect in Asian countries. Larger cohort of patients with CLAH is needed to correlate genotype and phenotype.

P1-d1-235 Adrenals and HPA Axis 1

Plasma matrix metalloproteinases activity in children with hypertension due to 11ß-hsd2 deficiency activity

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Background: No data exist in hypertensive children due to 11β-HSD2 deficiency activity and remodeling of the extracellular matrix. MMP-9 has significant effects on "profibrotic" proteins. MMP-2 degrades basement membrane proteins.
Objective: To elucidate the behavior of plasma MMP-9 and MMP-2 activities in hypertensive children with 11β-HSD2 deficiency activity compared with hypertensive children with normal enzyme activity matched by BMI percentile.
Subjects and methods: Hypertensive (n=102) children (5-16 years old) were studied. Systolic and diastolic blood pressure indexes (SBPi & DBPi) were calculated. Fasting serum cortisol (F) and cortisone (E) concentration were measured by RIA and the 11β-HSD2 activity was estimated by F/E ratio. 11β-HSD2 deficiency activity was considered when F/E ratio ≥4.3 (mean +2 SD, 93 normotensive subjects). MMP-9 and MMP-2 activities were evaluated by zymography. Of these hypertensive children 18/102 (17.6%) had F/E ratio≥4.3 (Group A, n=18). They were selected and were compared with a group of hypertensive children with F/E ratio< 4.3 (Group B, n=18) matched by BMI percentile. The results were expressed as median [Q1-Q3] and compared by Mann Whitney test.
Results: Group A and Group B showed similar age, 10.9 [7.7 - 12.9] vs 12.2 [10.3-14.1] years; P= 0.184). Group A had higher SBP index than Group B (1.24 [1.18-1.29] vs 1.14 [1.11- 1.18]; P < 0.001); but they had similar DBP index (1.25 [1.12-1.37] vs 1.17 [1.06-1.23]; P=0.078). Plasma MMP-9 and MMP-2 activities were higher in Group A than Group B (2.87 [2.02-3.09] vs 1.97 [1.37-2.34]; P=0.0124and 1.97[1.7-2.34] vs 1.55 [1.02-1.70]; p=0.018, respectively.
Conclusion: As far as we know, this is the first report showing an increase MMP-9 and MMP-2 activities in hypertensive children with high F/E ratio, suggesting that these patients have early and higher remodeling of the extracellular matrix.

P1-d1-236 Adrenals and HPA Axis 1

Adrenarche has no major association with dietary factors or physical activity

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Background: Adrenarche is associated with body weight, but only few studies have focused on diet and physical activity. In one previous study, dietary animal protein intake correlated with adrenal androgen secretion.
Objective and hypotheses: We examined the associations of diet and physical activity with serum DHEAS concentration in prepubertal healthy Finnish children aged less than 9 years. We hypothesized that nutrient intake and physical activity may contribute to serum DHEAS concentration.
Methods: Healthy prepubertal children (209 girls and 228 boys; age ± SD 7.6 ± 0.4 years in both sexes) taking part in The Physical Activity and Nutrition in Children (PANIC) Study were included in this study. Serum DHEAS concentration was determined by enzyme immunoassay. Nutrient intake was measured by 4-day food records. Physical activity was assessed by a questionnaire. Cardiorespiratory fitness was measured by a maximal exercise stress test on cycle ergometer. We used natural logarithmic transformation for DHEAS to normalize the skewed distribution. We analyzed determinants of serum DHEAS concentration by linear regression model adjusted for sex, age, and body fat percentage.
Results: Serum DHEAS concentration was not associated with intakes of total energy, fat, carbohydrates or animal protein. However, serum DHEAS

concentration was directly associated with vegetable protein intake (grams/day; standardized regression coefficient β 0.156, p=0.02) adjusted for sex and age. Further adjustment for body fat percentage had not effect on this association. Maximal workload per body weight, or total physical activity were not associated with serum DHEAS concentration.
Conclusions: Dietary factors or physical activity had no major associations with serum DHEAS concentration. Thus, apart from changes affecting body weight, modulating diet or physical activity may not significantly affect the risk of developing adrenal hyperandrogenism.

P1-d1-237 Adrenals and HPA Axis 1

Glucocorticoid replacement therapy in children with hypoadrenalism during physiological stress

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Background: The appropriate schedule of steroid coverage in hypoadrenal children during physiological stress is controversial.
Objective: The aim of this study was to evaluate the appropriateness of our steroid replacement therapy in hypoadrenal children during phy[siological stress.
Subjects and methods: We compared serum cortisol levels in hypoadrenal children with acute illness receiving stress doses of hydrocortisone (HC) replacement therapy with those in normal children with acute illness. In our schedule, a dose of 25 mg/m^2 HC was administered intravenously followed by constant intravenous infusion of HC at 100 mg/m^2/24hrs.
Subjects were 5 hypoadrenal children and 20 normal children with acute illness who needed hospitalization. Serum cortisol levels were measured on 30 minutes, 12 hrs and 24 hrs after the start of HC replacement therapy in hypoadrenal children, and on admission, 12 hrs and 24 hrs after the start of treatment in normal children.
Results: The median serum cortisol levels in hypoadrenal children on 30 minutes, 12 hrs and 24 hrs after the start of HC replacement therapy were 129.0, 44.4 and 45.6µg/dl, respectively. The median cortisol levels in normal children on admission, 12 hrs and 24 hrs after the start of treatment were 26.3, 15.1 and 12.3µg/dl, respectively. Serum cortisol levels in hypoadrenal children were significantly higher than those in normal children on all of the three points. However, serum cortisol level of a hypoadrenal child with serious illness was higher (82.5µg/dl, 12 hrs) than those in normal children (12 hrs).
Since serum cortisol levels in normal children on admission were relatively low comparing with those in previously reported seriously ill children, our subjects were considered to be moderately ill patients.
Conclusions: Our HC replacement schedule during physiological stress was considered to be appropriate in hypoadrenal children with moderate illness. However, it might be insufficient in those with serious illness.

P1-d1-238 Adrenals and HPA Axis 1

Bilateral adrenalectomy in 7 women and 1 girl with salt-wasting congenital adrenal hyperplasia (CAH) of difficult management

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Severe forms of CAH may occasionally be difficult to treat since, maintaining satisfactory adrenal suppression may be accompanied by hypercortisolism manifestations.
Objectives: To assess safety and efficacy of adrenalectomy in women with CAH with poor clinical outcome.
Patients and methods: Eight women with severe forms of CAH (21-hydroxylase deficiency). Bilateral adrenalectomy was performed by laparoscopy at a median age of 17.3(8.5-27.6) years.
Indications for adrenalectomy: 7 women had achieved adult height,were amenorrheic with hydrocortisone 15-19 mg/m2/day and, presented severe hypercortisolism under dexamethasone. The prepubertal girl had advanced bone age (+4 years).
Before surgery, I^{131}-cholesterol-scintigraphy seeking ectopic adrenal rests was performed in six patients.
Results: After surgery, hyperandrogenism disappeared in all.Postpubertal patients presented regular menses 2-3 months after surgery. In the prepubertal girl, breast development started 3 months after surgery and final adult height was 152 cm.No patient presented surgery-related complications. Six suffered adrenal crises and had high ACTH levels (>400 pg/ml) regardless of hydrocortisone treatment at 22 mg/m2/day and prednisone afterwards. Clinical manifestations improved with etilefrine and disappeared after 36-48 months in five patients and persist in one after 6 years. MR showed pituitary hyperplasia without signs of adenoma in 2 patients and was normal in 4.
Current status: 6.3(2-8.5) years after surgery. ACTH 231(16-1250) pg/mL, 17-OH-progesterone 1.4(0.7-3) ng/mL, testosterone 25 (< 10-64) ng/dL.Treatment: all patients prednisone 5-10 mg/day and six etilefrine.
Conclusion: Bilateral adrenalectomy in women with CAH could be indicated in selected patients after unsuccessful medical treatment. After adrenalectomy, hyperandrogenism disappeared and regular menses were restored. However, the risk of adrenal insufficiency symptoms of difficult management is high, though transient in most cases.

P1-d1-239 Adrenals and HPA Axis 1

Circadian rhythm (CR) of salivary cortisol (SAF) in children and adolescents using an ultrasensitive electrochemiluminescence immunoassay (ECLIA)

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Background: Only one study described SAF CR in childhood using ECLIA. In adults, a cut-off decrease of cortisol at night (D%)>50% was suggested for CR establishment. This evaluation is still lacking for SAF in children.
Objective: To evaluate CR of SAF in childhood using ECLIA.
Methods: Prospective, transversal study of SAF in 63 steroid-free children (2-18 ys;28 girls). Samples were obtained in the morning (mSAF; median: 8:00AM) and at night (nSAF, 11:00PM) using plastic tubes. The collection procedure was evaluated by a questionnaire. SAF was directly measured by ECLIA-Cortisol (Cobas-e411, Roche). Analytical performance of the SAF measurement was evaluated (CLSI evaluator protocols). SAF interindividual variation (iCV%) and the %D= [(mSAF-nSAF)/mSAF]x100 were calculated. Influence of age, gender and BMI on SAF and %D was assessed. Serum cortisol concentration (F) vs SAF correlation was assessed in other 40 independent patients.
Results: Total CVs< 15.3%, functional sensitivity=1.5 nmol/L, linearity (r=0.9945) and recoveries>80% were verified. SAF and F were significantly associated (r=0.75, p< 0.0001). 57/63 children referred no difficulties in salivary collection. mSAF and nSAF widely varied [mSAF iCV%: 49%, median;range (nmol/L): 16.1;2.9-36.7 and nSAF: 48%, 4.6;1.5-7.9, p< 0.0001). mSAF and nSAF did not vary with sex or BMI. nSAF (r= 0.54, p< 0.05) and %D (r= -0.58, p< 0.01) were associated with age. nSAF 97.5thcentile was 5.5 and 7.8 nmol/L for children < 10 years and >10 years, respectively (p=0.017). Interindividual D% variation was 22%. %D was >47% in children< 10 years and >36% in >10 years (p=0.004).
Conclusion: Ultrasensitive SAF measurement clearly demonstrated CR of cortisol without sex- or BMI-related changes. Our findings suggest that age should be taken into account when evaluating nocturnal levels of free cortisol in saliva. Preliminarily results also suggest that a %D>36 in children < 10 years and >47% in older children may reflect CR indemnity.

P1-d1-240 Adrenals and HPA Axis 1

Biochemical diagnosis of classic 3β-hydroxysteroid dehydrogenase deficiency in term newborns using urine metabolites of Δ5 steroids

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Background: Biochemical diagnosis of classic 3β-hydroxysteroid dehydrogenase deficiency (C3βHSDD) in newborns is theoretically not easy due to problematic diagnostic markers, Δ5 steroids and metabolites of them; those in newborns with ambiguous genitalia can be elevated such as classic 21-hydroxylase deficiency (C21OHD), P450 oxidoreductase deficiency (PORD), 11β-hydroxylase deficiency, congenital adrenal tumors, and disorders of sex development (DSD) of unknown origin with or without high serum 17-hydroxyprogesterone (H17OHP).
Objective: The objective of this study was to identify possible biochemical marker(s) for diagnosis of C3βHSDD in Japanese term newborns.
Subjects and methods: We recruited 6 groups.; one female with C3βHSDD, 41 females with C21OHD, 4 females and 3 males with PORD, 10 DSD with H17OHP, 97 DSD without H17OHP, and 1900 controls. All subjects were term Japanese newborn, and 5 groups except controls had ambiguous genitalia. We measured 13 metabolites of Δ5 steroids; 4 metabolites of pregnenolone (P5) including 3α,16α,20α-pregnenetriol, 3 metabolites of 17OHP5 including 15β,17α-diOHP5 and 6 metabolites of DHEA, in spot urines using gas chromatograph-mass spectrometry.
Results: Ranges of 3α,16α,20α-pregnenetriol and 15β,17α-diOHP5 (mg/g creatinine) in six groups were shown in Table.1. These two urine metabolites of Δ5 steroids could discriminate C3βHSDD from other 5 groups without overlap, while other 11 metabolites could not.

	3α,16α,20α-pregnenetriol	15β,17α-diOHP5
C3βHSDD	2.7,2.9	105,193
C21OHD	0.0-1.5	0.2-72
PORD	0.0-2.1	0.2-5.9
DSD with H17OHP	0.0-0.8	0.0-31
DSD without H17OHP	0.0-0.9	0.0-53
Controls	0.0-1.4	0.0-18

[Table.1]

Discussion: Urine 3α,16α,20α-pregnenetriol and 15β,17α-diOHP5 might be the biochemical diagnostic markers for C3βHSDD in term newborn with ambiguous genitalia.

P1-d1-241 Adrenals and HPA Axis 1

The novel mutation in the nicotinamide nucleotide transhydrogenase (NNT) gene with a classical case of familial glucocorticoid deficiency

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Background: Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder characterized by isolated glucocorticoid deficiency and patients therefore exhibit low serum cortisol with high plasma ACTH levels. Of FGD cases, 50% are caused by *MC2R*, *MRAP* or *STAR* genes, all encoding components of the ACTH signaling-steroidogenic pathway. More recently described defects in DNA replication and antioxidant genes, *MCM4* and *NNT*, expands the spectrum of pathways that can be pathogenic in FGD.
Objective and hypotheses: We aimed to identify causative mutations in cases presenting with FGD.
Methods: Consecutive cases with FGD were studied. The coding regions of the *NNT* gene is PCR-amplified and automatedly sequenced.
Results: A homozygous variant of p.G869D was detected in a classical case of FGD. This variant is not found dbSNP or 1000 genomes databases. *In slico* variant analysis programs SIFT and Polyphen2 both predict this variant to be deleterious. Functional study of the new mutation is ongoing.
Conclusions: The novel mutation of p.G869D is most probably responsible for FGD in this patient. This finding contributes to the genotype-phenotype correlation in FGD and reemphasizes the significance of *NNT* mutations in the pathogenesis of FGD.

P1-d1-242 Adrenals and HPA Axis 1

Cushing syndrome due to POMC secretion from a malignant yolk sac tumor in a two year old child

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Background: Cushing's syndrome due to ectopic ACTH production is extremely rare in children and is most often due to tumours in the chest. Rare cases of carcinoid tumours, neuroblastoma, phaeochromocytoma, pancreatic and ovarian carcinoma have been described. We describe an yolk sac tumour producing POMC causing paediatric Cushing's syndrome.
Case study: A 2yr old girl presented with rapid weight gain, hypertension, body odour, lethargy and moodiness. Urinary cortisol excretion was severely elevated. Cortisol was partly suppressed on low (22%) and high dose dexamethasone (43%) suppression tests. CRH test results suggested ectopic ACTH secretion. Imaging identified an abdominal tumour with marked peritoneal infiltration secreting α-feto protein (AFP, >300,000 kU/l). Histology initially revealed a malignant epithelial tumor, strongly expressing AE1/3 (a pancytokeratin marker) but not CD117, Oct3/4, CD56, desmin, WT1 and S100.
Post-translational processing of POMC generates ACTH, the N-terminal POMC fragment, and β-lipotropin (β-LPH) which is cleaved to produce γ-lipotropin and β-endorphin. Monoclonal antibodies recognising POMC (N1C11) or POMC and ACTH (A1A12) or the C-terminal splicing site of ACTH specifically (A2A3) were used to assess products produced by the tumour. POMC, but not ACTH, concentrations were increased, and these decreased during subsequent chemotherapy. Immunohistochemistry with these antibodies and E6B2, which recognises POMC and β-LPH but not ACTH, also suggested POMC, but not ACTH, production by the tumour. Our data suggest that either POMC binds to the adrenal ACTH receptor to stimulate cortisol production, or that POMC is cleaved within the adrenal to generate ACTH. Chemotherapy led to a temporary reduction in tumour mass, AFP and cortisol production. Repeat biopsy showed a yolk sac tumour.
Conclusion: We describe a malignant yolk sac tumour as a novel source of ectopic POMC production leading to Cushing's syndrome in a young girl.

P1-d1-243 Adrenals and HPA Axis 1

Comprehensive genetic analyses of primary adrenal failure of unknown etiologies: expanding phenotypic spectrum of *NNT* mutations

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Introduction: It is difficult to clarify the etiologies of primary adrenal failure without enzymatic defects by phenotypes and laboratory findings. Recently identified etiologies of primary adrenal failure led us to do comprehensive genetic analyses.
Objectives: Our objectives were to investigate the relative frequencies of single gene mutations (*CYP11A1*(*SCC*), *MC2R*, *MRAP*, *NNT*, *NR0B1*(*DAX1*), *NR5A1*(*SF1*), and *STAR*) in a Japanese cohort of primary adrenal failure of unknown etiologies (i.e. not caused by enzymatic defects) and to characterize the phenotypes.
Patients and methods: Twenty-nine patients with primary adrenal failure were enrolled. Deficiencies of 21-hydroxylase, 3β-hydroxysteroid dehydrogenase, 11β-hydroxylase, and P450 oxidoreductase were ruled out based on measurements of blood and urine steroid metabolites. Twenty-four patients had mineralocorticoid deficiency. Seventeen patients including four with disorders of sex development (DSD) had 46,XY and the remaining 11 had 46,XX. Nine patients had family histories of adrenal failure and/or unexplained death. The seven candidate genes were analyzed by PCR-based sequencing or next generation sequencing.
Results: Single gene mutations were identified in 17 patients; *NR0B1* in 9, *STAR* in 6, *NNT* in 2. Seven patients of the 9 carrying *NR0B1* mutations had family histories in male. The *STAR* mutation-carrying patients included one with 46,XY DSD with complete female genitalia, and 5 with 46,XX females. One patient harboring a homozygous mutation (Q40Kfs) in *NNT* exhibited normonatremia (serum Na 136.0-137.1 mEq/L, N=4) with relatively high plasma renin activity
(11.1-45.4 ng/mL/hr, N=6).
Discussion and conclusions: Mutations in *NNT*, *NR0B1*, and *STAR* accounted for more than half of our cohort. *NR0B1* mutations were relatively common in male patients, and the majority of them had family histories.*NNT* defects can present with mild mineralocorticoid deficiency, although such a phenotype has not been described previously.

P1-d1-244 Adrenals and HPA Axis 1

Utility of early morning cortisol and cortisone for the identification of patients with adrenal insufficiency during inhaled corticosteroid therapy for asthma

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Background: Biochemical abnormalities of the adrenal axis are reported commonly in children with asthma treated with inhaled corticosteroids (ICS), however episodes of adrenal crisis (AC) are rare. Case reports of patients who experience AC during ICS therapy report peak cortisol levels < 350nmol/L on standard provocative tests.
Objective and hypotheses: Early morning salivary cortisol (EMSC) and / or cortisone (EMSCn) can be used to screen patients treated with ICS for adrenal impairment.
Methods: 269 patients (160M, age 10.0yrs, 5.1 - 15.2) with asthma treated with ICS for >3 months collected saliva samples 30 minutes after waking for 3 consecutive days. On day 3 a low dose short Synacthen test (500ng Synacthen /1.73m^2) was performed.
Results: Peak cortisol in the LDSST was < 500nmol/L in 101 subjects (37.5%) and < 350nmol/L in 12 subjects (4.5%). EMSC and EMSCn had no predictive value for the identification of patients with a peak cortisol < 500nmol/L on the LDSST. For peak cortisol levels < 350nmol/L, a mean EMSC cut-off value of 6 nmol/L gave a negative predictive value of 98.8% and a positive predictive value of 9.5%. A minimum EMSCn cut-off value of 12.5 nmol/L gave a negative predictive value of 99.2 % and a positive predictive value of 30.1%.
Conclusions: EMSC and EMSCn show promise as screening tools for the identification of patients at greatest risk of AC during ICS therapy. Larger cohorts of patients with severe adrenal impairment now need to be studied to confirm or refute these data, and to improve the performance of the test.

P1-d1-245 Adrenals and HPA Axis 1

Definition of a practical sampling interval in 24h serum cortisol profiling to optimise treatment in children with 21-hydroxylase deficiency

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Background: Few centres employ serum 24h cortisol profiles to evaluate hydrocortisone replacement in children with 21-hydroxlyase deficiency (CAH-P450c21), and the sampling interval required to adequately assess replacement therapy has not been determined.
Objective: To define a practical sampling interval to assess hydrocortisone therapy, and to evaluate this approach in the optimization of therapeutic control.
Methods: We defined the optimal sampling interval in 36 children with CAH-P450c21. All children received hydrocortisone twice (n=22) or three times daily (n=14). Profiles with increasing sampling intervals (40, 60, 80, 100, 120,

140, 160, 180, 240 min) were generated. The periodicity of cortisol pulses was determined using Fourier Transformation and the effect of different sampling intervals on mean 24h serum cortisol evaluated using ANOVA. Using this information, we constructed 24h serum cortisol profiles in 96 children with CAH-P450c21. Cortisol concentrations were evaluated against predefined thresholds and in combination with serum 17OHP, androstenedione (A4) and growth parameters, guided adjustments in hydrocortisone therapy. Adjustments were assessed and dose compared with European data.
Results: Adequate definition of cortisol secretion was obtained with a sampling interval of 120 min. There was a 17% reduction in mean 24h cortisol concentration from 20 min sampling to 240 min sampling: 6.5 (1.9) ug/dL and 5.4 (1.6) ug/dL respectively. Following profiling, alterations to hydrocortisone treatment occurred in 61% of children and doses were significantly lower than a previous ESPE survey.
Conclusions: A maximum serum cortisol sampling interval of 120 min should be employed for assessment of hydrocortisone treatment adequacy in children with CAH-P450c21. In combination with other biochemical and clinical parameters, this technique enables fine-tuning of dosage and timing of hydrocortisone treatment.

P1-d1-246 Adrenals and HPA Axis 1

Atypical presentation of apparent mineralocorticoid excess

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Introduction: Apparent mineralocorticoid excess (AME), a rare inherited cause of hypertension, is due to a mutation in *HSD11B2* encoding the enzyme 11-β-hydroxysteroid dehydrogenase type 2. The resultant failure to convert cortisol to cortisone leads to excess mineralocorticoid activity. The typical presentation is severe and early-onset hypertension, often accompanied by growth failure, hypokalemic and renal stones. We present two sisters of Sudanese origin with AME in whom severe hypertension was absent early in the course.
Case study: Sister 1 presented at 3 years of age with failure to thrive, polyuria, hypokalemia, hypercalciuria, metabolic acidosis, nephrocalcinosis and secondary hyperparathyoidism. A renal tubulopathy was suspected, but the pattern was inconsistent with Gitelman or Bartter Syndrome. She was treated with potassium supplementation and a thiazide diuretic. She grew well. Sister 2 was noted to have same clinical and biochemical profile at age 18 months and was treated similarly. Blood pressures were considered normal. At ages 10 and 7, respectively, thiazide diuretic was replaced by amiloride with normalization of low serum potassium levels. At age 8, sister 2 was noted to be hypertensive (BP 160/120). Cardiac echogram showed concentric LVH. Serum aldosterone was suppressed at < 1 ng/dl (L, 5-80) with a plasma renin activity of 0.24 (0.5-5.9). She was treated with anti-hypertensives and BP normalized. DNA analysis was negative for Liddle Syndrome but positive for a novel AME mutation with a homozygous deletion in Exon 4 of the HSD11B2 gene in both sisters, predicting a premature termination of the protein at amino acid 239, of 405 amino acids in the wild type gene. A retrospective review revealed that BP had often been around 95th centile for age.
Conclusion: This report extends the clinical spectrum of AME. Age specific tables should always be used when considering if a child has hypertension.

P1-d2-247 Adrenals and HPA Axis 2

Diagnostic mysteries solved by exome sequencing

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Background: Six families with congenital endocrinopathies were unexplained by a candidate gene approach.
Objective: To provide a molecular diagnosis through next generation sequencing.
Methods: Whole exome sequencing followed by Sanger sequencing of potentially interesting sequence variants in probands.
Results: All families were explained. Two unrelated patients (9 and 12 in Nat Genet 44:740,2012) had mutations in *NNT* (nicotinamide nucleotide transhydrogenase); patient 12 has isolated glucocorticoid deficiency and patient 9 combined gluco- and mineralocorticoid deficiency: his more severe phenotype may be explained by additional variants in *ME3* (mitochondrial malic enzyme 3) (J Genom Exom, *in press*).
One patient (patient 5 in Table 6, JCEM 90:3243,2005) with combined gluco- and mineralocorticoid deficiency is a compound heterozygote for mutations in the steroid acute regulatory protein gene (*STAR*): p.W48X/p.R188C; this gene had not been tested, as imaging showed normal adrenals. Two 46,XY siblings with complete androgen insensitivity have a hemizygous intronic mutation in the androgen receptor, that had been missed by Sanger sequencing. Two siblings with a phenotype and a family history resembling androgen insensitivity (female external genitalia, 46,XY karyotype, two maternal aunts affected) have a heterozygous mutation in *NR5A1* (p.G77V), a gene that had not been tested due to normal adrenal function; the 46,XX mother of the probands developed ovarian failure at age 38, consistent with carrier status.
One patient with glucocorticoid deficiency due to apparent ACTH resistance has compound heterozygous mutations in the *POMC* gene, one of which (p.R8C) leads to the synthesis of an immunoreactive but bioinactive hormone (JCEM 98:736,2013).
Conclusions: Exome sequencing led to molecular diagnoses missed by a candidate gene approach. In congenital endocrinopathies, genome-wide analysis may establish etiology promptly, which is essential for counseling and management.

P1-d2-248 Adrenals and HPA Axis 2

Decreased 11β-hydroxysteroid dehydrogenase type 2 activity in neonates with 21-hydroxylase deficiency

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Background: Patients with 21-hydroxylase deficiency (21OHD) have an impaired cortisol biosynthesis, but it is unknown whether the metabolism of glucocorticoids differs between patients with and without 21OHD.
Objective and hypotheses: The objective of this study was to analyze the urinary glucocorticoid metabolism in neonates and infants with 21OHD.
Methods: We analyzed urinary steroid hormone profiles determined by gas chromatography-mass spectrometry of 95 untreated 21OHD neonates and infants, and 261 neonates and infants without 21OHD.
Results: 21OHD neonates exhibit elevated relative amounts of 11-hydroxy steroids like 5β-tetrahydrocortisol (THF) and 5α-THF on total glucocorticoid metabolism, whereas 11-oxo steroids like tetrahydrocortisone (THE) did not differ between neonates with and without 21OHD. As a consequence, neonates with 21OHD exhibit an increased ratio of (THF + 5α-THF)/ THE (median values: 0.11 vs. 0.03; $p < 0.0001$). This ratio correlated significantly with urinary concentrations of 17α-hydroxyprogesterone (17OHP) metabolites in neonates with 21OHD.
Conclusions: An elevated (THF + 5α-THF)/ THE ratio serves as a marker for decreased 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) activity. Our data indicate that neonates with 21OHD exhibit a decreased activity of 11βHSD2. Our data provide new insights into the pathophysiology of salt

wasting and regulation of sodium homeostasis in 21OHD. The inhibition of 11βHSD2 activity by 17OHP and its metabolites could contribute to phenotypic variability of sodium homeostasis in patients with 21OHD.

P1-d2-249 Adrenals and HPA Axis 2

Clinical follow-up in girls with non-classical congenital adrenal hyperplasia: can oral contraceptives replace steroid treatment?

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Background: Steroid therapy effectively suppresses elevated androgen levels associated with non-classical adrenal hyperplasia (NCCAH), but since it may induce side-effects some replace steroids with oral contraceptives (OCs) in girls who have completed growth.
Objective and hypotheses: To determine whether replacing steroids by OCs causes changes in clinical manifestations, androgen levels or metabolic parameters.
Methods: Studied retrospectively were NCCAH girls who either continued steroid therapy (n=32) or switched to OCs (n=12) after completing puberty and growth. Medical records were reviewed for clinical and laboratory parameters measured at growth completion (at 17.6±2.3 years for the steroid-treated (St) group, 18.7±2.3 years for the OCs group) and on 3 subsequent visits during the following 2 years. Findings were compared over time and between groups.
Results: At baseline, there were no significant between-group differences in BMI-SDS, androgen levels or prevalence of clinical polycystic ovary. The percentage of patients in the St and OCs groups who presented with acne, hirsutism and irregular menses was 53% vs 50% (p=0.6), 54% vs 36.4% (p=0.27) and 3.1% vs 16.7% (p=0.2), respectively. Over time, there was no significant difference in severity or prevalence of acne or hirsutism in either group or between groups. In the OCs group androstendione rose somewhat with a trend towards weight reduction, but the differences from the St group were not statistically significant. There were no significant differences in BMI-SDS, blood pressure, fasting glucose levels or lipid profile between groups at baseline and during follow-up.
Conclusions: In girls with NCCAH who complete growth, replacement of steroid therapy by oral contraceptives leads to regular menses, with no worsening of acne or hirsutism despite a trend towards increased androstenedione. Larger prospective, randomized studies, with longer follow-up are required to corroborate our findings.

P1-d2-250 Adrenals and HPA Axis 2

Evaluation of the hypothalamic-pituitary-adrenal axis and polysomnography in Prader-Willi children

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Background: Children with Prader-Willi Syndrome (PWS) are at risk for sudden and unexplained death during sleep. Hypothalamic dysregulation has been proposed as a common mechanism underlying both stress-induced central adrenal insufficiency (CAI) and central dysfunctional respiratory regulation during sleep. CAI was initially considered to be highly prevalent (60%), however, this finding could not be confirmed by later studies.
Objective and hypotheses: Analysis of CAI and sleep-related breathing disorders in children with PWS.
Methods: Retrospective study of the results of insulin tolerance tests (ITT) and glucagon tests (GT) in 19 children with PWS, and comparison to controls. Ten of these children had undergone at least one polysomnography (PSG), allowing correlation between sleep related breathing disorders and cortisol response.
Results: Only one out of 19 children tested with ITT and/or GT had CAI. The cortisol peak value showed a significant, inverse correlation with age (P = - ,601; p = ,006). A similar though non-significant correlation was present between cortisol increase during the stimulation test and age (P = - ,398; p = ,091). Similar correlations were found in controls. Sleep-related breathing disorders of central origin were detected in one patient, who exhibited a normal cortisol response. No relationship was found between peak cortisol or cortisol increase and central apnea index (respectively p = ,663 and p = ,097) or the other studied PSG parameters.
Conclusions: CAI assessed by ITT/GT is rare in children with PWS. Our data do not support the theory of an overarching hypothalamic dysregulation leading to both hypothalamic-pituitary-adrenal axis and central respiratory dysregulation. Given the facts that sudden, unexplained death in PWS occurs more at young age and higher cortisol responses are observed at younger age, a causal link with CAI is unlikely.

P1-d2-251 Adrenals and HPA Axis 2

Application of liquid chromatography-tandem mass spectrometry (LC-MS/MS) for diagnosis of congenital adrenal hyperplasia due to 11β-hydroxylase deficiency in a 5-year-old boy

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Introduction: In recent years, LC-MS/MS has emerged as an efficient method for multiple steroid profiling guiding diagnosis and treatment of adrenal diseases. We decribe the application of LC-MS/MS for rapid detection of a rare form of congenital adrenal hyperplasia.
Case study: A 5-year 4-month old Caucasian boy presented initially to a dermatologist for a one-year history of body odour and acne on the ears and cheeks, and rapid growth over the last 6 months. Initial work-up revealed an elevated 17-hydroxyprogesterone (17-OHP) of 14.2 nmol/L, performed by immunoassay at a commercial laboratory.
On physical exam at our centre, the patient was normotensive. Other than the mild acne, the height was 120.7 cm (97%ile, +1.9 SD for age). The patient had an increased penile length of 7 cm (>2 SD), with absence of pubic and axillary hair.
The bone age was advanced at 9 1/2 years. Biochemical analysis of specific adrenal steroids by LC-MS/MS, recently initiated at our centre, was performed on baseline and high-dose cosyntropin-stimulated plasma. Baseline 17-OHP was 2.5 nmol/L, increasing to 15.5 nmol/L at 60 min. The baseline 11-deoxycortisol was 63.5 nmol/L (normal, 0.2-6.0) and increased to 351.4 nmol/L (normal 2.8-10.4) at 60 min. Baseline samples revealed mildly elevated testosterone (1.6 nmol/L), androstenedione (8.5 nmol/L) and DHEAS (2.8 µmol/L). There was also a suboptimal cortisol response (194 nmol/L at baseline, 345 nmol/L at 60 min).
The patient was started on hydrocortisone replacement. The molecular genetic analysis of the *CYP11B1* gene demonstrated a variant of unknown clinical significance (IVS 1-11 T>A). CGH MicroArray results are pending.
Conclusion: This case highlights the advantageous use of LC-MS/MS for rapid detection and quantification of steroids related to rare forms of congenital adrenal hyperplasia beyond its use for newborn screening for this condition.

P1-d2-252 Adrenals and HPA Axis 2

Adrenal insufficiency in children and risk of hypoglycaemia: usefulness of continuous glucose monitoring

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Background: The glucocorticoid replacement treatment with oral hydrocortisone, recommended at 6-8 mg/m²/day in three doses, cannot reproduce the physiological cortisol circadian rhythm; in particular it does not eliminate the nocturnal hypocortisolemia. Consequently, children with adrenal insufficiency may have nocturnal hypoglycemia. We have recently demonstrated that continuous glucose monitoring (CGM) represents a valuable tool for detecting nocturnal hypoglycemic episodes in patients with combined ACTH and GH deficiency. Only one study described the use of CGM in adults affected by Addison's disease.
Objective and hypotheses: To verify if children with adrenal insufficiency show nocturnal hypoglycemia detectable by CGM.
Methods: Four children (one male and three females, age 2.9-17.8 years) with adrenal insufficiency (2 patients who underwent adrenalectomy because of recurrent Cushing disease, one with Familial Glucocorticoid Deficiency and one with isolated ACTH deficiency), treated with hydrocortisone at different doses, ranging from 6.5 to 17.8 mg/m²/day, underwent CGM for 48 hours. Morning fasting serum glucose was evaluated when CGM was removed. During the assessment, the patients were asked to maintain their usual life and eating habits.
Results: All four children showed normal fasting morning glucose serum levels, while CGM demonstrated hypoglycemia (glucose < 2.78 mmol/L) in 2 cases. Hypoglycemic episodes occurred in the early hours of the morning and lasted from 25 to 205 minutes.
Conclusions: Children with adrenal insufficiency can be at risk for nocturnal hypoglycemia. Hypoglycemic episodes happened in spite of replacement treatment with hydrocortisone at higher doses than those usually recommended. Further studies are required to confirm these data and investigate the correlation between hypoglycemia and hydrocortisone doses or other variables, such as the age or the cause of adrenal insufficiency.

P1-d2-253 Adrenals and HPA Axis 2

Three novel *CYP21A2* mutations in patients with nonclassical 21-hydroxylase deficiency

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Background: 21-OH enzyme is essential for cortisol biosynthesis. Its deficiency usually leads to androgen excess, consequently, to virilization and rapid somatic growth with accelerated skeletal maturation. Mutations in *CYP21A2* are responsible for different forms of 21-OH deficiency.
Objective and hypotheses: Investigate *CYP21A2* mutations in nonclassical (NC) patients.
Method: 47 families (115 individuals) were investigated by *CYP21A2* amplification and sequencing.
Results: Four groups have been identified: homozygous p.Val281Leu (36%); compound heterozygous p.Val281Leu and classical mutations (38%); compound heterozygous p.Val281Leu and NC mutation (17%); and compound heterozygous different NC mutations (9%). Three novel mutations were identified in two families. One affected child was compound heterozygous for p.Val281Leu and p.Leu12Met combined with p.Gln318*. She was born with clitoromegally without labioscrotal fusion; at 4.3 years she presented premature pubarche and bone age of 7.3 years. Both p.Asp377Tyr and p.Leu461Pro have been identified in a second child carrying p.Val281Leu in compound heterozygosis. She presented premature pubarche since 5 years old; at 6.4 years her bone age was 8.7 years. *In silico* prediction algorithms indicated these three new mutations as deleterious. Structural modeling analysis demonstrated each p.Asp377Tyr and p.Leu461Pro to cause important internal residue contact changes. Structural evaluations for p.Leu12Met was not investigated because it lies in the membrane interacting domain excluded from the CYP available crystallized structures.
Conclusions: Sixty out of 94 alleles (64%) carried p.Val821L among patients with NC 21-OH deficiency. Although known mutations occur in 34%, 2% alleles presented novel mutations. Two of them were identified in the same allele. Based on data presented here, all three novel variations are deleterious. *In vitro* studies on protein functional activity shall be performed to validate those data.

P1-d2-254 Adrenals and HPA Axis 2

N323K mutation of HSD3B2 gene in two siblings: sexual ambiguity limited to male gender

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Background: Deficiency of 3β-HSD results in a reduced production of mineralocorticoids, glucocorticoids and sex steroids. The symptoms usually occur in the neonatal period, with adrenal insufficiency. Although mild virilization has been reported in female with 3β-HSD deficiency, usually external genitalia are normal in females and variably undervirilized in males.
Objective: To report the phenotype and genotyping of two siblings (brother and sister) with 3β-HSD deficiency.
Patients and methods: We studied a brother and a sister (five and one years old respectively) born from consanguineous parents (third cousins) of Maghreb origin, with very high level of 17-OHProgesterone at CAH neonatal screening. A strong increase of urinary adrenal steroid metabolites' Δ5/Δ4 ratio through MS analysis and very high serum level of 17-OHPregnenolone and DHEA suggested a 3β-HSD deficiency. The detection of a homozygous missense mutation, p.N323K (c.969T>G) changing an Asparagine to Lysine located at C-terminal region of HSD3B2 had confirmed the diagnosis. Both siblings have a salt wasting form at the age of 15 days, treated successfully by fludrocortisone: 1) normal natremia (135 mmol/L) with hyperreninemia (447μU/ml) at day 12, followed by hyponatremia (128 mmol/L) at day 15 in the brother; 2) hyponatremia (< 130 mmol/L) with hyperreninemia (> 600 μU/L) at day15. The male had penoscrotal hypospadia and descended testis at birth. The sister, born four years later, showed normal genitalia with a normal anogenital ratio (anus-vulvar fourchette/anus-clitoris = 0.5).
Conclusions: N323K mutation of the *HSD3B2* gene should be a severe mutation. In vitro studies should confirm this deduction. Diagnostic of 3b-HSD deficiency should be suspected at birth in two situations: a 46,XY DSD or a 46, XX newborn without virilization of external genitalia, both having a positive CAH neonatal screening (high 17-OHProgesterone).

P1-d2-255 Adrenals and HPA Axis 2

Different clinical presentation of X-linked congenital adrenal hypoplasia in four patients with new mutations in the *NR0B1* gene

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Background: X-linked congenital adrenal hypoplasia (AHC) is a potentially life-treatening condition caused by mutations in *NR0B1* gene. This gene, situated on the short arm of chromosome X, encodes for a nuclear receptor protein (DAX-1) which regulates the development of adrenal cortex, gonads, hypothalamus and pituitary gland. Although rare, AHC represents the most frequent cause of primary adrenal insufficiency, with an estimated incidence of 1/12.500 births.
Objective and hypotheses: Clinical and biochemical features of four Romanian children with different clinical presentation of AHC were analyzed

to underline the importance of a prompt diagnostic approach.
Methods: Case 1 was a preterm newborn presenting with severe salt wasting crisis. Clinical evaluation showed normal male genitalia excluding congenital adrenal hyperplasia due to 21-OH deficiency. Pedigree analysis demonstrated two maternal cousins with infancy onset adrenal insufficiency (case 2 and 3). Case 4 was a twelve year old boy admitted for vomiting and dehydration associated with severe hyponatremia (121 mEq/l) and hypochloremia (89 mEq/l). Family history showed an older brother died for an undefined severe dehydration at the age of five suggesting the hypothesis of AHC.
Results: Molecular studies revelaed a new frameshift mutation (c.1058_1059delCC) of the *NR0B1* gene resulting in a premature stop codon and then in a truncated protein in case 1,2 and 3. A small deletion (c.745_746delAA) producing a truncated protein was identified in case 4. X-linked inheritance of the defect was confirmed in both families with the detection of the same mutation through the maternal line.
Conclusions: We identified two mutations in the *NR0B1* gene never described before. Our study suggests that age at onset and clinical presentation of the disease may be various. AHC should be considered in both newborns and older children with primary adrenal failure, in order to avoid latency between first symptoms and diagnosis.

P1-d2-256 Adrenals and HPA Axis 2

11β-hydroxylase deficiency: functional characterisation of three novel CYP11B1 mutations

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Background: 11β-hydroxylase (P450c11) deficiency (11OHD) causes the second most common form of congenital adrenal hyperplasia (CAH), one of the most common autosomal recessive inherited endocrine diseases. The 11OHD incidence ranges between 5% and 15% of CAH cases in non-consanguineous and consanguineous populations (Muslim and Jewish Middle eastern), respectively.
Objective: The aim of the study was to investigate functional consequences of three novel CYP11B1 mutations; p.His125Thrfs*8 (c.372delG) and p.Leu463_Leu464dup (c.1387_1392dupCTGCTG) detected in Turkish, and p.Ser150Leu (c.449C>T) in Moroccan patients suffering from classic and non-classic 11OHD, respectively.
Method: The mutations were functionally characterised by using a HEK293 cell *in vitro* expression system comparing wild-type (WT) with mutant activity. Mutant proteins were examined *in silico* to study their effect on the three-dimensional structure of the protein.
Results: The mutations p.His125Thrfs*8 and p.Leu463_Leu464dup have no residual activity. The frameshift mutation p.His125Thrfs*8 terminates the translation at the B-C loop of the protein. The variant p.Leu463_Leu464dup produces an additional half turn of the L-helix and leads to a displacement of the following protein structure. The p.Ser150Leu mutation detected in a patient with a non-classic phenotype showed partial functional impairment with 19% of WT activity. The change to p.Leu150 does not lead to obvious steric problems with neighbouring residues *in silico*.
Conclusions: The increasing data on non-classic CYP11B1 mutations helps to increase the knowledge on structure-function interaction in cytochrome-P450 enzymes. Functional characterizations are important to predict the phenotypic outcome and provide precise information for clinical and genetic counselling.

P1-d2-257 Adrenals and HPA Axis 2

Hypercortisolism results in a differential delay in bone maturation of the bones of the wrist and hand

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Background: Childhood hypercortisolism results in specific impairment of enchondroplasia, as observed in tubular bones of the hand, representing the legs, and chondral osteogenesis, as observed at the carpal cuboid bone, representing the vertebrae.
Objective and hypotheses: To determine how glucocorticoids (GC) differentially affect the two processes.
Methods: A bone age x-ray (BA) was performed in 58 patients with Cushing Syndrome and 63 age-matched healthy controls (normal height, weight, and growth velocity, suffering no chronic illnesses and taking no medications). Each bone was individually scored by the standards of Greulich and Pyle, and the ratio of chronologic age (CA) to BA calculated for each bone. The mean CA/BA ratio between groups was analyzed for each bone or group of bones using the Students t-test with unequal variances. Multivariate regression analysis was used to determine the factors that were contributing most to these differences.
Results: Highly significant differences ($P < 0.001$) were seen between carpal bone maturation, greatest for the lunate and scaphoid. Smaller differences ($P < 0.05$) were seen between metacarpals and distal phalanges, whereas differences for the proximal and middle phalanges were not significant. Multivariate analysis of patients with Cushing syndrome showed that there was no correlation between the degree of BA delay and either the urinary free cortisol or the disease duration. BA correlated with gender for all bones, while age was only significant for proximal and middle phalanges. However neither age nor gender significantly influenced inter-group results.
Conclusions: Hypercortisolemia interferes with linear growth mostly by inhibiting chondral osteogenesis by a mechanism similar to that seen in glucocorticoid-induced osteoporosis, while, to a lesser extent, it delays enchondroplasia. BA reading must include the carpal bones for chondral osteogenesis, representing vertebral maturation.

P1-d2-258 Adrenals and HPA Axis 2

Corticotropin tests for assessment of the hypothalamus-pituitary-adrenal axis in patients with Prader-Willi syndrome

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Background: Hypothalamic-pituitary anomalies are well proven in Prader-Willi syndrome (PWS), consistent with deficiency of many pituitary hormones. In this context, we have previously demonstrated that central adrenal insufficiency (CAI) may be part of the PWS phenotype. However, the diagnostics of CAI is critical and debated, due to the lack of fully reliable tests. Several studies have looked at the clinical usefulness of the low dose (1 µg) synacthen test (LDSST) compared to the conventional dose (250 µg) test (SDSST) in patients with pituitary disease. Actually, the dose used in the conventional SDSST is considered supraphysiological and might produce a deceivingly adequate cortisol (F) response. Nevertheless, other reports suggested no difference between the LDSST and SDSST in patients with multiple pituitary hormone deficiency.
Objective: The aim of this study was to compare the F response to both LDSST and SDSST in a group of patients with PWS.
Methods and patients: Thirty-three subjects with genetically confirmed PWS, 18 males, aged 1.8-37. yrs, were studied. All patients underwent LDSST and SDSST. In each test blood samples for F determination were taken at 0 and 30 min. For both tests, to diagnose CAI we selected a F cut-off point of < 18.1 µg/dl.
Results: The mean peaks of F after LDSST and SDSST were 24.3±1.1 µg/dl (mean±SE) and 25.0±1.3 µg/dl, respectively (p=0.6). The average increase of F from baseline was 11.7±0.9 µg/dl (LDSST) and 12.8±1.2 µg/dl (SDSST) (p=0.4). The LDSST and SDSST produced 27 normal and 1 (adult) abnormal concordant results. Three patients (1 children and 2 adults) who passed the SDSST failed the LDSSD. On the contrary, 2 adults failed the SDSST but passed the LDSSD.
Conclusions: Our data seem to confirm that CAI diagnosis in PWS patients cannot be based on a single test alone. In this light, repeat hypothalamus-pituitary-adrenal testing is fully justified in this situation.

P1-d2-259 Adrenals and HPA Axis 2

Molecular genetic analysis of CYP21A2 gene and genotype-phenotype correlations in Croatian patients with classical form of 21-hydroxylase deficiency

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Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is autosomal recessive disorder caused by mutations of CYP21A2 gene. It is classified as classical (salt wasting-SW and simple virilizing-SV) and nonclassical(NC).
Objective and hypotheses: To describe CYP21A2 gene mutations and evaluate genotype-phenotype correlation in Croatian patients with classical CAH.
Methods: Molecular analysis of CYP21A2 gene was performed in 93 patients (60 males/33 females; 66 SW/27 SV) and 193 first-degree relatives (134 parents, 59 siblings). Allele specific PCR was used to detect point mutations and Southern blot and gene sequencing to detect deletions and conversions. Genotypes were categorized into three groups according residual enzymatic activity (0-no, A-minimal and B-about 2%).
Results: Mutations were found in both alleles in 91 probands. Despite clinical and hormonal evidence of CAH, in one patient mutation in only one allele and in one patient no mutations at all were found after detailed gene sequencing. Mutation frequency was: I2G 35.5%, del/conv 19.4%, R356W 15.1%, I172N 11.3%, Q318X 5.4%, del 8bpE3 2.1%, Ex6 cluster 1.6%, R426H 1%, P30L 1%, R483P 0.5%. Positive predicted phenotype in group 0 was 100%, in A 86% and in B 75%. Intrafamilial phenotype variability was found in two families. Analysis of CYP21A2 gene in family members revealed 7 new patients.
Conclusion: This is the largest study of CYP21A2 gene mutations in classic 21-OHD patients in Southeast Europe. Distribution of CYP21A2 gene mutations in Croatians is in concordance with reports from other European countries, except the high incidence of R356W mutation (15.1%), rare in all reported populations except in Asians. Genotyping larger number of Slavic patients should reveal whether mutation R356W is ethnic specific for this population. Partial genotype-phenotype correlation and intrafamilial phenotype variability suggest that phenotype prediction should be made with caution.

P1-d3-260 Adrenals and HPA Axis 3

Mutations of the *KCNJ5* gene in patients with hypertension and increased aldosterone response to ACTH

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Background: Aldosterone secretion by the adrenal *zona glomerulosa* is regulated by angiotensin II, K^+ and ACTH. Somatic and germline mutations of the *KCNJ5* gene, expressed in the *zona glomerulosa* and encoding the Kir3.4 inward rectifying K^+ channel, have been identified in patients with Familial Hyperaldosteronism (FH) type III. FH type I, on the other hand, is due to a chimeric gene originating from the unequal crossing over between the *CYP11B1* and *CYP11B2* genes.
Objective and hypotheses: The aim of this study was to investigate the presence of *KCNJ5* gene mutations or the *CYP11B1/CYP11B2* chimeric gene in patients with hypertension and an increased aldosterone response to ACTH but no evidence of primary aldosteronism.

Patients and methods: We studied 23 hypertensive patients aged 35-68 years with normal findings on adrenal computed tomography scan and increased aldosterone response to ACTH (0.03 µg, iv). Using the 97.5% of CI of aldosterone concentrations and the aldosterone/renin ratio (ARR) of a population of 61 healthy controls, we defined increased aldosterone response the presence of both aldosterone >1300 pmol/L and ARR > 77 pmol/mIU. Genomic DNA was isolated from peripheral blood leucocytes in all subjects. The coding region of *KCNJ5* gene was PCR- amplified and sequenced. The chimeric gene *CYP11B1/CYP11B2* was PCR amplified as previously described.
Results: Two novel *KCNJ5* heterozygous mutations were detected; the p.V259M c.775G>A in exon 2 and the p.Y348N, c.1042T>A in exon 3. The in silico analysis showed that the mutations were deleterious and that amino acids V259 and Y348 are highly conserved among species. The chimeric gene *CYP11B1/CYP11B2* was not detected in any of our patients.
Conclusions: Two novel mutations of the *KCNJ5* gene were detected in two hypertensive patients with an increased aldosterone response to ACTH stimulation. These findings indicate that the K^+ channel might be involved in the pathophysiology of idiopathic hypertension.

P1-d3-261 Adrenals and HPA Axis 3

Low body mass index (BMI) at birth is associated with early adiposity rebound in 21-hydroxylase deficiency patients

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Background: 21-hydroxylase deficiency (21-OHD) is a most common type of congenital adrenal hyperplasia. Major clinical problems of 21-OHD are adrenal crisis, virilization of external genitalia, short stature and infertility due to adrenal androgen excess. Additionally, recent literatures have suggested that 21-OHD patients have a risk for obesity and metabolic syndrome. Recently we have conducted longitudinal analysis of auxological data in 21-OHD patients, and discovered that timing of adiposity rebound (AR), when BMI starts to increase after its nadir, was significantly precipitated comparing to normal control of children. It has been recognized that premature AR can be a risk for obesity and metabolic syndrome in adult age. Identifying factors that precipitates AR will reveal the mechanisms of obesity and metabolic syndrome of 21-OHD patients, enable to develop the efficient approach for the prevention metabolic syndrome.
Subjects and methods: We retrospectively analyzed 23 (male: 12 cases, female: 11 cases, SW: 14 cases, SV: 9 cases) classical 21-OHD patients who were discovered by neonatal screening and followed up at least until the age of ten years.
Results: There were no significant relationships between the therapeutic regimen and timing of AR. The serum level of 17-OHP sampled before the treatment during neonatal period did not show any association with premature AR, however, patients of salt wasting form showed earlier AR than simple virilizing form (p=0.02). Gestational age, birth-weight and birth-height were not associated, whereas, low body mass index (BMI) at birth was significantly associated with AR precipitation (p=0.0004).
Discussion and conclusion: In 21-OHD patients, timing of AR is associated with BMI at birth and with severity of the disease, suggesting environmental factors during fetal period affect timing of AR and could increase risks for obesity and metabolic syndrome in adult age.

P1-d3-262 Adrenals and HPA Axis 3

Mutation analysis of *CYP21A2* and correlation between genotype - phenotype in Vietnamese patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Background: Congenital adrenal hyperplasia (CAH) is one of the most common inherited metabolic disorders. The most common form of CAH (95%) is caused by mutations in *CYP21A2*, the gene encoding the adrenal steroid 21-hydroxylase enzyme (P450c21).
Objective and hypotheses: To identify the mutations in the *CYP21A2* gene in Vietnamese patients with CAH and attempt a genotype-phenotype correlation.
Methods: Molecular analysis was performed using PCR, multiplex ligation-dependent probe amplification and direct sequencing of PCR products of the *CYP21A2* gene in 134 CAH patients. Correlation between phenotype and genotype was evaluated based on identified mutations and clinical manifestations.
Results: Mutations were identified in 254 alleles. Ten different causative mutations were identified in *CYP21A2* including two novel mutations. The most frequent genetic defect was the IVS2-13A/C>G
(89 alleles; 35%) mutation, followed by Large deletion (68 alleles; 27%); p.R356W (45 alleles; 18%); p.I172N (22 alleles; 9%). The rarer mutations were novel one p.R484fsX541 (6 alleles; 2.4%) and novel one p.S125X (4 alleles; 1.6%); p.Q318X (8 alleles; 3.1%); p.R426C (7 alleles; 2.8%) and c.920-921insT (p.L307Frameshift) (4 alleles; 1.6%). The majority of patients (105 cases; 78.4%) were homozygotes. Seven cases were compound heterozygous. Genotype accurately predicted phenotype in 95.7 and 100% of patients with salt-wasting and simple virilizing, respectively.
Conclusions: The spectrum of mutations of the *CYP21A2* gene in Vietnamese patients is comparable to the some reported in other Asian population. Large deletion accounts for nearly one-third of the genetic defects. Therefore, laboratory should include methods for detecting point mutations as well as large deletions. Genotype-Phenotype correlation was high in the studied patients.

P1-d3-263 Adrenals and HPA Axis 3

A novel SF1 mutation in a boy with late onset adrenal insufficiency, normal external genitalia and hypergonadotrophic hypogonadism

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Background: The steroidogenic factor 1 (SF1, NR5a1) gene is expressed in the gonads, adrenals, pituitary gland and hypothalamus. The SF1 mutation phenotype varies: primarily sexual differentiation disorders and, less frequently, adrenal failure, fertility disorders and premature ovarian insufficiency.
Objective and hypotheses: To report an unusual clinical presentation of a novel SF1 mutation.
Patient and results: A boy presented at age 7 yrs with weakness, dizziness and vomiting over the past 48 hours. Three similar episodes were reported in the past 2 years; they all led to dehydration and subsequent hospitalization, but no specific diagnosis was made. Pertinent laboratory findings were: Na 124 mEq/L, K 5.1 mEq/L, serum cortisol 10.7 µg/dL, plasma ACTH 1450 pg/ml (NV < 50), plasma renin activity >36 ng/ml/hour (NV 0.5-9.6). The diagnosis of Addison disease was made and substitution therapy with hydrocortisone and 9a-fluorocortisone was initiated. At age 14.5 yrs there was

concern for nonprogression of secondary sex characteristics. His height was on the 3rd percentile (Bone Age 12.5 yrs). The external genitalia were normal, pubic hair development was Tanner I and testicular volume bilaterally 8 ml. Serum testosterone was 83 ng/dl, FSH 24 mIU/ml, LH 1.7 mIU/ml, AMH 16.9 pmol/L (NV 25-450). DNA sequencing of the SF1 gene disclosed a novel heterozygous mutation (p.D309N in exon 5). *In silico* analysis characterized the mutation as "damaging". No molecular defect was detected in the DAX or StAR genes. The asymptomatic father was a carrier of the same SF1 mutation; no defect was detected in the mother. Functional studies of the SF1 mutation are still in progress.
Conclusions: The novel heterozygous SF1 mutation (p.D309N) reported herein affects both adrenal and testicular steroidogenesis and Sertoli cell function, but has no obvious effect on the pituitary or the hypothalamus and is associated with normal external genitalia and late-onset manifestations.

P1-d3-264 Adrenals and HPA Axis 3

Implementation of a LC-MSMS method for routine determination of 17-hydroxypregnenolone and dehydroepiandroterone-sulfate and its application in endocrine diagnoses

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Background: Reliable assays for determination of dehydroepiandrosterone-sulfate (DHEAS) and 17-hydroxypregnenolone (17OH-Preg) are indispensable for the differential diagnosis of pediatric endocrine conditions in the post-RIA era.
Objective: To establish a LC-MSMS method for the simultaneously determination of 17OH-Preg and DHEAS and to determinate age and pubertal specific reference ranges for children.
Methods: 0.1 mL plasma was extracted by solid phase extraction (SPE) and analyzed using an UPLC-MS/MS in MRM mode. Reference data was determined by using left-over samples from routine paediatric blood tests. 505 children were categorized into the age groups 0-11 months, 1-6 years, 7-12 years, 13-15 years, and 16-18 years. As an example for its clinical application plasma from patients with 3ßHSDII deficiency due to mutations and obesity were measured.
Results: The method was linear up to 600 nmol/l for 17OH-Preg and 6000 nmol/L for DHEAS. The limit of detection was 0.05 nmol/l for 17OH-Preg and 0.5 nmol/l for DHEAS. We compared our assay with RIA assays (DHEAS) (Siemens) and RIA with prior extraction (17OH-Preg). The coefficients of determination were 0.95 for DHEAS and 0.93 for 17OH-Preg. Both hormones showed a characteristic decline in the neonatal period and an increase at the age of 7-9 years. Patients with 3ßHSDII deficiency showed 15-to 100-fold multiples of the median (MOM) of the 17OH-Preg reference value and slightly elevated DHEAS values. In patients with obesity we measured 4-fold MOMs for 17OH-Preg and 3-fold MOM for DHEAS.
Conclusions: We developed a robust, fast and reliable method for analyzing of DHEAS and 17OH-Preg in the daily routine. Reference data allow diagnosing pediatric endocrine disorders. Delta-5 steroids are elevated in obesity.

P1-d3-265 Adrenals and HPA Axis 3

A novel *StAR* splice site mutation in a 46,XX patient with lipoid congenital adrenal hyperplasia

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Background: Steroidogenesis produces mineralocorticoid, glucocorticoid and sex steroids from cholesterol in the adrenal glands and gonads. StAR transports cholesterol from the cytosol to the mitochondria. Loss of StAR function causes lipoid congenital adrenal hyperplasia (LCAH), with impaired synthesis of all adrenal and gonadal steroids manifesting as adrenal insufficiency and female external genitalia irrespective of genetic sex.
Objective and hypothesis: We identified a novel mutation in a *StAR* acceptor splice site position and hypothesized that it produces an aberrant mRNA splicing.
Patient and methods: A newborn girl of consanguineous parents was admitted because of a choking crisis with hypotonia. She had normal external female genitalia without hyperpigmentation, and presented mild dehydration, hyponatremia, hyperkalemia and hypoglycemia. She showed low plasma cortisol, 17OH-progesterone, DHEA-S, androstendione and aldosterone and high ACTH and plasma renin activity consistent with the diagnosis of primary adrenal insufficiency. Adrenal capsule antibodies were negative and very-long-chain fatty acids normal. Imaging showed normal adrenal glands and karyotype was 46,XX.
We analysed *MC2R*, *MRAP*, *CYP11A1* and *StAR*. The *StAR* splice mutation was studied *in vitro* by a minigene experiment in COS-1 cells. Splicing was assessed by RT-PCR for *StAR* cDNAs on extracted total RNA of wild type (WT) versus mutant.
Results: *StAR* presented a novel homozygous mutation in the acceptor splice site of intron 4, c.466-1G>A. The mutant *StAR* minigene was processed to a shorter cDNA fragment than the WT and contained the full sequence of exons 4 and 6, skipping exon 5. Biocomputational studies revealed that exon 5 is crucial for the StAR-cholesterol interaction.
Conclusions: *StAR* c.466-1A skips exon 5, which is essential for the function of StAR. This is a loss-of-function mutation that causes the severe LCAH phenotype in our patient. Thus far, all 11 *StAR* splice mutations cause a severe phenotype.

P1-d3-266 Adrenals and HPA Axis 3

Molecular mechanisms of action of the natural human glucocorticoid receptor (hGR) mutant hGRαT556I causing primary generalised glucocorticoid resistance

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Background: Primary Generalized Glucocorticoid Resistance (PGGR) is a rare genetic condition caused by mutations in the hGR gene, which alter hGR action and reduce tissue sensitivity to glucocorticoids. A new case of PGGR caused by a novel heterozygous point mutation in the hGR gene, which resulted in threonine (T) to isoleucine (I) substitution at amino acid position 556 in the ligand-binding domain of the receptor, has been recently reported in a patient with adrenal incidentaloma.
Objective and hypotheses: To delineate the molecular mechanisms of action of the natural mutant receptor hGRαT556I.
Methods and results: Compared with the wild-type receptor (hGRαWT), the mutant receptor hGRαT556I demonstrated a 22% reduction in its ability to transactivate the glucocorticoid-inducible MMTV promoter in response to dexamethasone. Western Blot analyses showed equal protein expression of

hGRαWT and hGRαT556I, indicating that the above findings did not reflect differences at the protein expression levels. Dexamethasone-binding assays showed that the affinity of the mutant receptor hGRαT556I for the ligand was 2-fold lower than that of the hGRαWT (21.3 ± 4.09 nM *vs.* 10.8 ± 0.99 nM). In subcellular localization and nuclear translocation studies, both the hGRαWT and hGRαT556I were predominantly localized in the cytoplasm of cells in the absence of ligand. Addition of dexamethasone resulted in slower translocation of the mutant receptor hGRαT556I into the nucleus (50 min), compared with the wild-type receptor (15 min).
Conclusions: The natural mutant receptor hGRαT556I alters glucocorticoid signal transduction through multiple molecular mechanisms.

P1-d3-267 Adrenals and HPA Axis 3

Pitfalls in the diagnosis of 11β-hydroxylase deficiency - new insights from four patients carrying novel *CYP11B1* mutations

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Background: Steroid 11β-hydroxylase (CYP11B1) deficiency (11OHD) is the second most common form of congenital adrenal hyperplasia (5-8%). 11OHD is associated with adrenal insufficiency, hypertension, and 46,XX disorders of sex development. Mild 11OHD manifests later in life and is clinically indistinguishable from nonclassic 21-hydroxylase (CYP21A2) deficiency (21OHD).
Objective: To elucidate the role of 3 novel *CYP11B1* gene variants on the pathogenesis of 11OHD.
Patients: Patient P1 was a 46,XX baby born with ambiguous genitalia (Prader stage IV). Patient P2 was a 46,XY boy manifesting with signs of hyperandrogenism at age 3 yrs. Patient P3a was a 46,XY boy presenting with gynaecomastia at age 7.7 yrs and other clinical and biochemical features indicative of 21OHD. However, no *CYP21A2* mutations were found; at age 11.3 yrs, elevated 11-deoxycortisol (S) concentrations were measured. Advanced bone age and genital skin hyperpigmentation were noted in his younger brother (P3b) at age 3.3 yrs. Biochemical investigations showed elevated concentrations of 17OHP, S and androgens in all patients.
Methods: *CYP11B1* genetic analyses were performed. The ability of the novel *CYP11B1* mutations to convert S to cortisol was assessed in COS7 cells co-overexpressing wild-type (WT) or mutant *CYP11B1* and adrenodoxin.
Results: Genetic analyses revealed patients were compound heterozygotes for *CYP11B1* mutations. The novel R453W and a *CYP11B2/CYP11B1* chimeric gene were found in P1, the severe R374Q and the novel R453W in P2, and the novel R138C and L407F in P3a and P3b. Functional analyses demonstrated that R453W and L407F completely abolished CYP11B1 activity, and R138C only retained 10% of WT activity.
Conclusions: A broad 11OHD phenotypic spectrum is described. Similarly to 21OHD, 5-10% residual CYP11B1 activity appears to result in a moderate phenotype. Our study emphasizes the risk of delayed diagnosis in patients with 11OHD, which may impact on personalised health care provision.

P1-d3-268 Adrenals and HPA Axis 3

Newborn screening for congenital adrenal hyperplasia in Tokyo, Japan: lessons learned from 23 years' experience

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Background: In 1989, newborn screening program for congenital adrenal hyperplasia (CAH) was introduced in Tokyo. To date, more than two million neonates were screened and 101 CAH patients were identified. There are few large studies of CAH screening in Asian countries, then, we report CAH screening in Tokyo, lessons learned from our 23 years' experience.
Methods: From 1989 to 2010, total 2101246 neonates were screened. Enzyme-linked immunosorbent assay was used, and cut off level were adjusted for gestational age and for birth weight. The data was obtained by follow-up survey.
Results: In our follow up survey, no fatal cases were identified.
Four hundred two cases (0.021%) were referred to clinical hospitals due to the positive results of the screening, and 101 patients were diagnosed as having CAH (the prevalence: 1/20804). In addition to 90 patients that were diagnosed as 21-OHD (salt wasting form: 70, simple virilizing form: 14, non classical form: 6), one 3ß-HSDD patients were discovered by the screening. The types of other 11 patients were not known.
The sex assignments of 93 patients (male: 54, female: 39) were available in the survey. The 39 female cases included 8 cases whose sexes were correctly assigned by the screening, i.e., the assignment of two patients were changed from male to female, and 6 patients were assigned as female according to the result of the screening.
The birth weight and the gestational age were 3195.8+/-390.7g (2380~4384g) and 38.9+/-1.34 weeks (36~42 weeks), respectively. All patients that showed high level of 17-OHP (>20ng/ml) on the first test were classical type. While all non-classical type patients showed mildly elevated (=< 19.4ng/ml) of 17-OHP on the first test.
Discussion: Our findings suggest that newborn screening of CAH was useful, especially for sex assignment and preventing fatal cases. The prevalence of CAH, birth weight and gestational age were consistent with the previous reports.

P1-d3-269 Adrenals and HPA Axis 3

A novel mutation of the human glucocorticoid receptor *(hGR)* gene causing mild primary generalised glucocorticoid resistance

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Background: Primary Generalized Glucocorticoid Resistance or Chrousos syndrome is a rare, familial or sporadic condition characterized by generalized, partial tissue insensitivity to glucocorticoids because of neutralizing mutations in the human Glucocorticoid Receptor (*hGR*) gene.
Objective and hypotheses: The aim of this study was to present a new case of Chrousos syndrome caused by a novel mutation of the *hGR* gene.
Methods: A 17 year old male presented with long-standing fatigue but no clinical manifestations of hyperandrogenism or mineralocorticoid excess. Endocrinologic evaluation revealed elevated 08:00h plasma ACTH 9202.9 pg/ml; normal range (nr): 7-63 pg/ml] and cortisol (30.46 μg/dl; nr: 6.2-19.4 μg/dl) concentrations and resistance of the hypothalamic-pituitary-adrenal (HPA) axis to Dexamethasone suppression. DNA was isolated from peripheral blood leukocytes and the entire coding region of hGR gene was PCR-amplified and sequenced.
Results: A novel one base pair heterozygous insertion at nucleotide 1870, c.1870_1871insG was detected in exon 6 of the *hGR* gene. The insertion was not present in the parents of the patient indicating that this was a *de novo* mutation. This insertion creates a frameshift, resulting in a premature stop codon at amino acid 626, p.A624GfsX2. Therefore, it leads to a loss of 151 amino acids of the C terminal polypeptide and approximately 50% of the ligand-binding domain (LBD) of the hGRα. *In silico* analysis employing the Mutation T@ster software showed that this insertion is a disease causing molecular event.
Conclusions: We report a novel insertion of the *hGR* gene resulting to a premature stop codon and the loss of 50% of the LBD of hGRα. Functional studies are being carried out to investigate the molecular mechanisms through which this mutation affects glucocorticoid signal transduction.

P1-d3-270 Adrenals and HPA Axis 3

Clinical, laboratory and genetic evaluation in 46,XX patient with P450c17 deficiency

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Background: Congenital adrenal hyperplasia due to P450c17 deficiency is a rare autosomal recessive disease.
Objective and hypotheses: To report the clinical, laboratory, genetic and ovarian imaging of 46,XX patients.
Population: We evaluated eighteen patients belonging to 12 families.
Results: Most patients had primary amenorrhea (83%) and 89% of the patients had blood hypertension at diagnosis. We observed a high incidence of emotional disorders such as depression and anxiety (13/18). All patients showed elevated LH and progesterone levels, and decreased androgen levels. The ultrasound assessment showed an increase of at least one of the ovaries in 75% of the patients before treatment and ovarian macrocists in 56%, three of them reported previous surgery indicated by twisting or ovarian rupture. The molecular study showed that 17 patients have inactivating mutation in the *CYP17* gene and 1 in POR gene. Two novel mutations were identified in *CYP17* gene, the p. R362H in exon 6 and an intron3-éxon4_deletion (g.3997_4026del). The most prevalent mutation in *CYP17* was p.W406R, followed by p.P428L. The patients were treated with dexamethasone, estrogen and progesterone with ovarian volume reduction.
Conclusions: We emphasize the importance of basal progesterone assay to diagnosis and the high prevalence of psychiatric disorders and ovarian macrocists with risk of twisting, in 46,XX patients whit P450c17 deficiency.

P1-d3-271 Adrenals and HPA Axis 3

Evaluation of cognitive function and behavioural performances in girls with non-classical congenital adrenal hyperplasia

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Background: Impaired cognitive function and behavioural disorders have been reported in girls with classical congenital hyperplasia (CAH), possibly due to prenatal androgen exposure.
Objective and hypotheses: Aim of this study was to investigate whether the same disorders may be observed even in girls with non-classical (NC) CAH, where the role of prenatal hyperandrogenism could be excluded.
Patients and design: We administered the following neuropsychological tests to 9 girls with NC CAH (median age 12.9 years, IQR 11.2-15.5) and to their age-matched healthy sisters (10 girls, median age 14.5 years, IQR 13.0-16.3): Leiter-R, 16 Personality Factor Inventory (16PF), Multidimensional Self Concept Scale (MSCS), Child Behaviour Checklist (CBCL). Dose of glucocorticoid treatment, 17-OHP and Androstenedione levels during the last year were chosen as indicators of postnatal androgen excess.
Results: Both full-scale IQ ($p < 0.05$) and reasoning subtest ($p < 0.01$) were significantly lower in the patient group, when compared to control group [89.7 (75-103.5) vs 103.2 (91-115) and 86 (67-99) vs 100 (97-118), respectively]. No other significant differences were found. In NC-CAH group, no correlations between IQ levels and androgen levels were found.
Conclusions:
a) even in the NC CAH girls is present an impaired cognitive function, probably related to a postnatal androgen excess;
b) the behavioural changes, seen in girls with classical CAH and related to prenatal androgen excess, does not seem to be present in NC-CAH patients;
c) studies on larger NC-CAH populations should be performed for confirming our preliminary findings.

P1-d1-272 Autoimmune Endocrine Diseases 1

Defective transitional B cell compartment in APECED patients: correlation with the development of clinical symptoms of the disease

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Background: Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is a rare autosomal recessive syndrome due to mutations in *AIRE*, characterized by autoimmune endocrinopathies and mucocutaneous candidiasis. It is accompanied by serum auto-antibodies related to the escape of autoreactive T cells from tolerance mechanisms, but recent studies highlight T independent mechanisms involved in the pathogenesis of the disease.
Objective and hypotheses: The aims of our study have been:
1) characterization of the B cell compartment during asymptomatic and disease active phase in one young APECED patient,
2) characterization of requirements of transitional B cells to be activated and
3) analysis of serum cytokines.
Methods: Transitional B cell subsets have been stimulated in the presence of BAFF and IFNg. Proliferation and differentiation to plasma cells have been evaluated by CFSE dilution and ELISA assay respectively. Serum cytokines levels were evaluated by a Millipore bioplex kit.
Results: We analyzed B cell subsets in the youngest patient at the time when he was still asymptomatic, and two years later when he developed the disease. We observed a significant depletion of the transitional B cell compartment with the development of clinical signs of the disease. In term of transitional B cell subsets characterization we observed that expansion and differentiation of transitional B towards plasma cells is selectively enhanced by the presence of IFNg and BAFF.
Conclusions: Our hypothesis is that autoantibodies generation in APECED patients is mediated by an altered peripheral B cell selection not entirely dependent from T cells. We propose a BAFF and IFNg dependent mechanisms on the immature transitional B cell compartment to drive them towards plasma cell fate, with an increase risk of developing auto-reactive non proper selected plasma cells.

P1-d1-273 Autoimmune Endocrine Diseases 1

Investigation of osteopontin levels and genomic variation of osteopontin and its receptors in type 1 diabetes mellitus

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Background: Diabetes mellitus (DM) is a common, chronic, metabolic syndrome characterized by hyperglycemia. Failure in self tolerance towards b cells in diabetes pathogenesis involves a series of complex events that are governed by environmental and genetic factors.
Objective and hypotheses: According to importance of osteopontin (OPN) in Th1 cell development, the aim of this study is evaluation of serum level and gene polymorphism of osteopontin in Iranian type 1 diabetic children.
Methods: This is a case-control study on 87 type 1 diabetic children & 86 healthy ones. Blood sample of both group were checked for osteopontin level. The single gene polymorphism were genotyped by RFLP analysis for osteopontin rs1126772, its receptor integrin a4 (ITGA4) rs 1449263, and CD44rs8193.
Results: The serum level of OPN in diabetic children was significantly higher in patients than controls ($p=0.023$). But there is no significant relationship

between osteopontin rs1126772 (p=0.79), its receptor integrin a4 (p=0.31) and CD44 rs8193 (P=0.45) and type 1 diabetes.
Conclusions: The higher amount of OPN was seen in type 1 diabetic children. According to its role in Th1 activation, it might be initiated or progress T1DM when genetically susceptible individual predisposed an environmental insult. However, the 3 SNPs of OPN and its receptor have not associated with T1DM. Our study does not exclude the possibility that other SNPs of OPN and its receptors might be associated with this disease. More studies are needed to clarify this issue.

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Prevalence of early allergic sensitization in **children with HLA-conferred susceptibility to type 1 diabetes**

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Background: The role of HLA haplotypes conferring risk for type 1 diabetes (T1D) in the presumed imbalance between Th1/Th2 cells in allergic and autoimmune diseases is not well defined.
Objective and hypotheses: We set out to study the prevalence of early atopic sensitization and its possible impact on growth in children with HLA-conferred susceptibility to T1D. We hypothesized that the prevalence of atopic sensitization is lower and its influence on growth less obvious in the subjects carrying the high-risk HLA genotype DR3-DQ2/DR4-DQ8.
Methods: In Finland and Estonia, the growth of 497 children with HLA-conferred susceptibility to T1D was monitored from birth up to the age of 2 years and expressed in SD score (SDS) using WHO growth reference data. Weight and height of children testing negative or positive for at least one allergen-specific IgE (≥0.70 IU/l) out of seven tested at the age of 18 months were compared using the t-test. According to their HLA haplotypes, the subjects were divided into three risk groups for T1D (high/moderate/low), and the difference in the prevalence of allergen-specific IgE antibodies was compared between those groups with the chi-square test.
Results: The proportion of children with at least one specific IgE antibody was highest (16%) in the low-risk group and lowest (10%) in the moderate-risk group, but the difference remained non-significant (p=0.13). There were no significant differences in mean height and weight SDS at the age of 3, 6, 12, 18 or 24 months between children with signs of early atopy and those without it. Similar results were seen when the Estonian and Finnish cohorts were analysed separately.
Conclusions: Early atopic sensitization does not seem to be associated with HLA genotypes conferring risk for T1D. The were no signs that early atopic sensitization should affect children's growth during the first 2 years of life.

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Endocrine autoimmunity in Turner syndrome: retrospective analysis of 67 patients and review of the literature

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Background: Turner syndrome is a condition caused by numeric and structural abnormalities of the X chromosome, and is characterized by a series of clinical features, the most common being short stature and gonadal dysgenesis. An increased frequency of autoimmune diseases as well as an elevated incidence of autoantibodies has been observed in Turner patients.
Objective and hypotheses: We present the retrospective analysis of the incidence of autoimmunity in 67 patients affected by Turner syndrome.
Methods: Karyotypes were 45,X (n= 32); mosaicism (n=18); isochromosomes (n=7), delections (n=5), X-ring (n=5).SRY was detected by FISH (fluorescence in situ hybridisation).TgAb,TPOAb by chemiluminescence method, parietal cells (PCA), adrenal cortex (ACA), islet cell by indirect immunofluorescence, steroid 21-hydroxylase (21-OH), GADA, IA2, insulin by radioimmunoassay (RIA) were assayed. IgA anti-gliadin and anti-transglutaminase were measured.
Results: 27 patients presented autoimmune manifestations (40.29%). Overall 15 patients had Hashimoto's thyroiditis, 12 patients had preclinical autoimmune disease with positive anti-thyroid antibodies.According to karyotypes autoimmunity percentages were 46.8%,22.2%,71.4%,60% and 20% in 45X,mosaicism, isochromosome, deletions and X-ring, respectively. Across ages, autoimmunity percentages were 21.4%,46.1%,37.5% in 0-9.9, 10-19.9 and 20-29.9 age ranges, respectively.
Conclusions: Our data show an increased risk of autoimmunity in TS as reported in previous investigations and a preponderance of thyroid autoimmune disease.No increase of autoimmunity was observed with age as opposite to other authors.Neither represented karyotypes were associated at statisticaly significant levels with the presence of autoimmunity in contrast to previous finding.We observed thyroid autoimmunity in 21.42% of patients patients before the age of 9.9,in contrast with studies reporting no presence in thyroid autoantibodies/ hypothyroidism before the age of 8.

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Time lying down and energy expenditure are important determinants of vascular health in children with type 1 diabetes

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Background: Meeting national standards for diet/activity aid in cardiovascular disease prevention in type 1 diabetes (T1D). There is limited data on the association between vascular health, diet/activity in T1D children.
Objective and hypotheses: To evaluate association between vascular health, diet/activity in T1D children.
Methods: 53T1D children, no complications (age 14.2yrs(2.1), 26 males) had vascular health evaluation (Flow/glyceryl trinitrate mediated dilatation [FMD/GTN] and carotid intima media thickness [cIMT]), energy intake (EI)[Australian Child and Adolescent Eating Survey], energy expenditure (EE) and activity [SenseWear physical activity monitor], body composition (DEXA) and biochemical/clinical variables from baseline data of RCT(ANTRN12611000148976).
Results: T1D duration 5.9y(4), HbA1c 8.8%(1.2), BMIz-score 1.0(0.6), daily EI 10750 (2354) KJ, daily EE 9604 (2001.5) KJ, time lying down 8.92(1.1)h, systolic blood pressure (SBP) 113.2(7.2), diastolic blood pressure (DBP) 63.8 (5.2), FMD 6.15 (4.3), GTN 23.72 (6.2). FMD independently and positively related to lying down time (r=0.34, p=0.01,B coefficient =1.47, p=0.006) and not other variables.

	r	p-value
EE	-0.37	0.006
EI	-0.44	0.001
Waist circumference	-0.32	0.018
Fat free mass (DEXA)	-0.39	0.004
Protein	-0.34	0.017
Fat	-0.37	0.008
Saturated fat	-0.35	0.011
CHO	-0.39	0.004
Sugars	-0.34	0.015

[Table 1 GTN associations]

GTN independently related to EE(B coefficient=-0.0011, p=0.04) and DBP(B coefficient =0.32, p=0.01). cIMT independently related to EE (B coefficient=0.0002,p=0.007) and diabetes duration (B coefficient=0.0058, p=0.04) but no other variables.
Conclusion: Time lying down and EE are important determinants of vascular health in T1D children.

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21-hydroxylase and interferon omega autoantibodies in Turner syndrome

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Background: An increased frequency of autoimmune diseases and an elevated incidence of autoantibodies have been observed in Turner syndrome (TS).
Objective and hypotheses: Indirect immunofluorescence (IIF) has not been able to demonstrate autoantibodies against the adrenal cortex in TS. We asked if the more sensitive radioimmunosorbant assay employing recombinant human 21-hydroxylase was able to identify autoantibodies against 21-hydroxylase, (21OH-Ab) in TS patients; 21-hydroxylase is the major adrenal cortex autoantigen in patients with autoimmune Addison's disease. Moreover, TS patients were tested for antibodies against interferon omega (IFNw-Ab), a marker for autoimmune polyendocrine syndrome 1 (APS 1) where autoimmune Addison's disease is one of the main components.
Methods: Blood samples from 144 karyotyped TS (11-62 years) were assayed 21OH-Ab and IFNw-Ab using in vitro transcribed and translated autoantigen. An index was calculated with a cut-off point of 57 and 200 for 21OH-Ab and IFNw-Ab, respectively.
Results: Autoantibodies against 21-hydroxylase with low indices were present in 6 TS patients (4.2%); none had INF-omega autoantibodies. Overall, the TS patients had a mean age of 31.6 years (range 11.2-62.2). 53% (n=77) had the karyotype 45X. Hypothyroidism was recorded in 9% (n=20), coeliac disease in 1.4% (n=2), and type 1 diabetes mellitus in 0.7% (n=1). The six TS patients with 21-hydroxylase antibodies had a mean age of 32.7 years (range 17.7-44.7). Two had the karyotype 45 X. One patient had hypothyroidism, but none had clinical apparent Addison's disease.
Conclusions: 21-hydroxylase autoantibodies can be detected by using RIA in some patients with TS. These findings add to previous studies showing a high proportion of TS with an array of different autoimmune antibodies. Whether any of the autoantibody-positive TS patients will eventually develop Addison's disease remains to be seen.

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The prevalence of ZnT8 autoantibodies in Czech children at onset of type 1 diabetes mellitus and dynamic changes of serum ZnT8 autoantibody concentrations over time

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Background: Zinc transporter (ZnT8) is an important islet autoantigen in type 1 diabetes (T1D).
Objective and hypotheses: The prevalence of autoantibodies to zinc transporter 8 (ZnT8Ab) in Czech children at onset of type 1 diabetes mellitus (T1D) and dynamic changes in ZnT8Ab concentrations during follow up were studied. The value of ZnT8Ab measurements in the diagnosis of T1D was assessed.
Methods: Serum samples from 227 children with newly diagnosed T1D and from 101 control children without diabetes were analysed in retrospective cross-sectional study. 171 samples from 116 patients with diabetes were analysed retrospectively in a follow up study at (median) 1, 3, 5 and 10 years after T1D onset. ZnT8Ab were measured using a bridging ELISA while antibodies to glutamic acid decarboxylase (GADAb), to the insulinoma antigen 2 (IA-2Ab) and to insulin (IAA) were measured by radioimmunoassays.
Results: ZnT8Ab were detected in 163/227 (72%) of children at T1D onset and in 1/101 (1%) of control children. 16/227 (7%) T1D patients were antibody negative based on three antibodies (GADAb, IA-2Ab and IAA) and this was reduced to 10/227 (4.4%) ($p < 0.05$) after inclusion of ZnT8Ab measurements. 142/227 (63%) of children were positive for at least three antibodies and the most common combination was IA-2Ab, GADAb and ZnT8Ab. ZnT8Ab concentrations decreased over time after T1D onset and positivity and titre of ZnT8Ab correlated with IA-2Ab.
Conclusions: ZnT8Ab ELISA showed 72% disease sensitivity and 99% specificity at T1D onset. Measurements of ZnT8Abare important for T1D diagnosis and should be included in the panel of autoantibodies tested at the onset of T1D.
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Cerebellar ataxia in a patient with autoimmune polyglandular syndrome type 1

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Introduction: Neurological disorders are rare in patients with autoimmune polyglandular syndrome type 1 (APS-1). Cerebellar ataxia has been previously described in a single case of APS-1.
Case study: A 21-year-old male, homozygous for R257X AIRE mutation, has hypoparathyroidism since 8, hypothyroidism since 11, chronic candidiasis since 13 and adrenal failure since 16. At 20 years he complained of diplopia and progressive gait ataxia which led to partial disability during next 6 months. MRI revealed an irregular enhanced mass (12x15 mm) of the left cerebellum hemisphere. Partial surgical resection was performed. Histology and immunohistochemistry analysis could not distinguish between atypical lymphoproliferative syndrome (LSS) and inflammatory pseudo-tumor. Tests for CMV, HHV, EBV in serum and CSF were negative. The anti-GAD antibody test was positive (196 U/mL). Test for antibody to cerebellar Purkinje cells was negative. The bone marrow aspirate was normal. The patient did not receive a specific treatment during next six months after the surgery. Slow clinical progression with mild progression of infiltrative process on MRI were seen during this period. After the treatment with prednisone 2mg|kg|day for the next month positive dynamics on MRI was noticed, however, without clinical improvement. We supposed that the diagnosis of autoimmune encephalitis with pseudo-tumor was most probable, but LSS also could not be excluded. The chemotherapy with Rituximab and Cyclophosphamide was started.
Conclusions: This is a second case of cerebellar ataxia in APS-1 patient described to date. In contrast to the first case with positive anti-Purkinje antibodies and vermal atrophy, in our patient we revealed mass lesions of the cerebellum that was difficult to distinguish between autoimmune encephalitis and LSS. We suppose that immune defects due to AIRE-gene mutations could lead to the development of the unusual autoimmune encephalitis and neoplasia of the brain.

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Vitamin D status and the effects of vitamin D treatment in children with vitiligo

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Background: Vitiligo is an autoimmune depigmentation disorder. Reduced vitamin D levels have been associated with several autoimmune diseases.
Objectives: To evaluate serum 25-hydroxyvitamin D [25(OH)D] levels in children with vitiligo and to establish the efficacy of oral vitamin D treatment with topical corticosteroid on the repigmentation of vitiligo.
Methods: Thirty (18 boys) new-onset vitiligo (age 10.9±3.3years) patients without systemic autoimmune diseases and 30 sex- and age-matched healthy children (18 boys) as controls (age 10.8±3.3years) were included in the study. Lesion sizes and levels of 25(OH)D, parathyroid hormone (PTH), calcium, phosphorus, alkaline phosphatase were measured at baseline and sixth month. Vitamin D deficiency were defined as 25(OH)D level < 20µg/l. Both patients and controls who diagnosed vitamin D deficiency were treated with oral vitamin D for six months. The patients were treated with topical corticosteroid at the same time.
Results: Serum 25(OH)D levels of patients with vitiligo and controls were 26,6±18,3µg/l and 22,8±13,5µg/l, respectively (p> 0,05). 25(OH)D levels were increased and PTH levels were decreased significantly after six months of treatment in children with vitamin D deficieny. In patients with vitiligo who received oral vitamin D treatment with topical treatment (n= 14), lesion size decreased from 66,1±58,3cm² to 48,0±52,6cm² after 6 months of treatment (p< 0,001). In patients who received only topical corticosteroid ointments (n= 16), lesion size increased from 34,8±48,1 cm² to 53,5±64,9cm² (p= 0,002).
Conclusions: Although we did not establish decreased baseline serum 25(OH)D levels in children with vitiligo, we found a marked reduction in lesion size in vitiligo patients who received vitamin D treatment with topical corticosteroid ointments. Although we had a small sample size, we suggest that vitamin D treatment besides topical corticosteroid ointments have been successful in the repigmentation of vitiligo.

P1-d1-281 Autoimmune Endocrine Diseases 1

Cytokines and high sensitive CRP before and after meal-induced hyperglycemia in children with type 1 diabetes

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Background: Good metabolic control reduces the risk of vascular complications in type 1 diabetes (T1D). Post meal hyperglycemia has been associated with low grade inflammation and endothelial dysfunction in adults with type II diabetes, and is considered a risk factor for vascular complications.
Objective and hypotheses: To compare the levels of seven pro-inflammatory cytokines, high sensitive c-reactive protein (hsCRP), and the anti-inflammatory cytokine - transforming growth factor beta (TGF-β), in children with T1D and healthy controls. To compare the cytokine and hsCRP levels before and after meal-induced hyperglycemia in children with T1D. We hypothesized that hyperglycemia increases the level of the pro-inflammatory cytokines and hsCRP and reduces TGF-β.
Population and methods: We included 84 (46 females) children with T1D, age 14.2 (11.2;15.7) years, HbA_{1c} (SD) 7.9 (1.1) %, a pre-meal blood glucose (BG) below 10 mmol / l, and a meal increase in BG of more than 10 mmol / l. Sixty-nine children (37 females), age 12.1(10.6;13.1) years served as controls. The pro-inflammatory cytokines, hsCRP and TGF- β were measured before and 90 minutes after a standard meal.
Results: Three of seven pro-inflammatory cytokines and hsCRP were significantly higher, and TGF-β was significantly lower in children with T1D with normal BS compared to healthy controls. TGF β decreased significantly 90 minutes after a standard meal, but so did the pro-inflammatory cytokines - tumour necrosis factor beta, monocyte chemotactic protein 1, and tumour necrosis factor receptor type 1.
Conclusions: Children with T1D have increased pro-inflammatory cytokines and hsCRP and reduced TGF- β despite normal BG, indicating a constant low grade inflammatory state. High BG decreases TGF- β further, while some pro-inflammatory cytokines also decreases, the effect of which may outweigh each other. Post meal hyperglycemia did not seem to increase the pro-inflammatory state in children with T1D.

P1-d1-282 Bone, Growth Plate and Mineral Metabolism 1

Brittle bones caused by mutations in *WNT1* - new gene, new therapeutic approach?

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Background: Osteogenesis imperfecta (OI) is a hereditary disease with high variability of clinical symptoms, formerly associated with dominant mutations in *COL1A1/A2*. Recently several recessive causative genes have been discovered including *WNT1*.
Objective and hypotheses: Two children of consanguine families presenting with symptoms of OI (increased fracture rate, reduced bone mass) were examined. Analysis of the known causative genes for OI revealed no mutations. The objective was to identify the genotype leading to the signs of OI.
Methods: Patients showed no typical signs of a pathologic collagen production (dentinogenesis imperfecta, hypermobility of joints, hearing loss, discoloured sclera). Serum calcium, alkaline phosphatase levels, urinary deoxypyridinoline/creatinine were in the age-related normal range. Further characteristics are displayed in Table 1.

Clinical finding	Patient 1	Patient 2
Age at first presentation (years)	2.8	0.45
Time of follow up (years)	8.8	4.6
Age at start of bisphosphonate treatment (years)	4.9	3.5
Weight at first visit (kg) / BMI (SD)	16.0 / 18.4 (1.9)	6.9 / 18.0 (1.5)
Height at first visit (cm) / (SD)	92 / -2.5	62 / -0.3
Mobility at last visit BAMF (points)	7	6
Last DXA ap spine: BMD (g/cm2) / z-score	0.700 / -1.2	0.342 / -5.2

[Table 1. Clinical findings]

To identify the underlying genotype whole-exome sequencing and additional functional analyses were performed.
Results: In patient 1 a homozygous missense mutation in WNT (c.529G>T) was detected causing a reduction of the canonical WNT signalling in luciferase assay (38%). In patient 2 a homozygous donor-splice-site-mutation (c.624+4A>G) in WNT1 was identified reducing the amount of *WNT1* transcript in PCR.
Conclusions: Loss of function mutations in the osteoblast formating WNT1 pathway cause autosomal recessive "OI". These findings might offer new therapeutic approaches (e.g. Antisclerostin as Sclerostinantibody promising osteoblast formation) to realize a translational treatment concept even in a rare disease like OI.

P1-d1-283 Bone, Growth Plate and Mineral Metabolism 1

Compound heterozygous mutations of *SLC34A3* can cause idiopathic hypercalciuria without rickets: novel mutations detected in a sporadic case of a girl with idiopathic haematuria

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Introduction: Mutations in *SLC34A3* cause hereditary hypophosphatemic rickets with hypercalciuria (HHRH). Heterozygotes for the mutations usually show only hypercalciuria or no symptoms. On the other hand, compound heterozygotes or homozygotes of the mutated alleles mostly show clinical features of rickets. Indeed, biallelic mutations of the gene have been identified in several patients with typical HHRH features. We report novel compound heterozygous mutations of *SLC34A3* detected in a Japanese girl suffering from hypercalciuria without rickets.
Case study: A 3-yr-old girl was admitted to our hospital because of microscopic hematuria. Laboratory data showed slightly elevated calcium levels and the reduced inorganic phosphorus level of 2.5 mg/dL. Maximal renal phosphate reabsorption per glomerular filtration rate was depressed to 2.4 mg/dL. Elevated serum $1,25(OH)_2D$ levels and hypercalciuria were also observed. These laboratory data were consistent with HHRH. However, she had no clinical features of rickets or familial history of any skeletal disease, mineral disorders or hypercalciuria. Genetic analysis of the patient revealed novel compound heterozygous mutations [c.IVS3 +1 G>A from her mother and c.1234 C>T (a missense mutation substituting tryptophan for arginine at codon 412) from her father] in *SLC34A3*. These mutations were absent in 50 Japanese control subjects.
Conclusion: We report here the first patient with compound heterozygosity of *SLC34A3* mutations and a normal skeletal feature. The results indicate that mutations of *SLC34A3* result in idiopathic hypercalciuria without rickets in some cases. Since orally administrated phosphate is predicted to improve symptoms of these patients, mutation screening of *SLC34A3* should be considered for patients with idiopathic hypercalciuria of unknown etiology. Compound heterozygous mutations of *SLC34A3* can be responsible for idiopathic hypercalciuria without skeletal lesions.

P1-d1-284 Bone, Growth Plate and Mineral Metabolism 1

A family with autosomal dominant hypocalcaemia with sensorineural hearing impairment and low urine excretion of calcium

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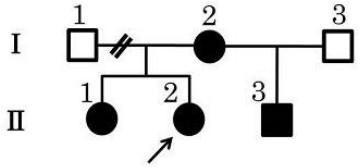
Introduction: Autosomal dominant PTH-deficient hypoparathyroidism consists of heterogeneous disorders, including 22q11.2 deletion syndrome, HDR syndrome, and autosomal dominant hypocalcemia (ADH). HDR syndrome is caused by haploinsufficiency of *GATA3* and characterized by sensorineural deafness and renal dysplasia. ADH is caused by an activating mutation of *CASR* and characterized by relatively high urine excretion of calcium.
Case study: The proband, a 4-yr-old Japanese girl, visited us due to repeated febrile and afebrile convulsions. The proband, two siblings, and their mother were diagnosed as autosomal dominant PTH-deficient hypoparathyroidism (Figure1 and Table 1). Of note was that 1. two of them had sensorineural hearing loss and 2. three had low urine excretion of calcium (Urine Ca/Cr 0.02-0.05).
All coding regions of *GATA3* and *CASR* were amplified from genomic DNA by PCR, followed by direct sequencing. FISH analysis on 22q11.2 region was performed.
The Proband, two siblings, and their mother had no mutations in *GATA3* nor 22q11.2 deletion. All these four subjects had a heterozygous missense mutation c.622C>T (p.P221L) in *CASR*, previously reported as an activating mutation in ADH.
Conclusion: Clinically HDR syndrome was highly likely, judging from autosomal dominant PTH-deficient hypoparathyroidism, sensorineural hearing loss, and low urine excretion of calcium. The diagnosis of ADH was, however, confirmed by the identified *CASR* activating mutation. In autosomal dominant PTH-deficient hypoparathyroidism the difficulty in clinical differential diagnosis of ADH and HDR syndrome is possible, requiring molecular analysis.



Case	I 2	II 1	II 2	II 3
Age (year)	31	7	4	2
Ca (mg/dL)	7.2	7.2	8.3	7.5
P (mg/dL)	6.2	6.2	7.3	6.5
Intact PTH (pg/mL)	12	11	7	9
Urine Ca/Cr	NA	0.05	0.03	0.02
Sensorineural hearing loss	NA	+	+	−
Renal dysplasia	−	−	−	−
Dysmorphic features of 22q11.2 deletion syndrome	−	−	−	−

NA : not applicable

[Figure1 and Table1: Family tree and clinical data]

P1-d1-285 Bone, Growth Plate and Mineral Metabolism 1

Hyperparathyroidism and low sclerostin are the main causes of smaller and weaker bones in obese children

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Background: Obese children show an unfavorable bone geometry and a bone of low quality and reduced strength at a non-weight bearing skeletal site.
Objective and hypotheses: To investigate the role played by the Wnt/β-catenin signalling pathway and its inhibitors sclerostin and Dickoff (Dkk)-1 in the negative influence of fat mass on bone.
Methods: This was a cross sectional observational study performed in 44 (males 26, females 18) obese subjects, aged 11.5 ± 2.6 years. Bone geometry (i.e. cross sectional area (CSA), cortical area (CA), medullary area (MA) and bone strength (BBRI), according to the formula $[D^4 - d^4 / D])$ was evaluated at the level of the 2nd metacarpal bone, using digitalized X-rays.We also assessed PTH (1-84), 25-OHD3, serum carboxy-terminal telopeptide of telopeptide of collagen-1 (CTX) as a marker of bone resorption, procollagen-1 (P1NP) as a marker of bone formation, bone alkaline phospatase (BAP), sclerostin and Dickoff (Dkk)-1. Bone geometry data are expressed as SDS. Differences of the geometry data were evaluated against zero, while the biochemical values of the obese group were compared with a control group of 20 subjects of normal weight and height.
Results: CSA, CA and MA were all significantly smaller than in controls as well as BBRI. PTH and CTX were significantly increased in the obese children; on the contrary sclerostin was significantly decreased (see table). P1NP was also raised, although it did not reach statistical significance.
Conclusions: Obese children have a high-turnover bone metabolism, leading eventually to smaller and weaker bones. High PTH and low sclerostin levels seem to be responsible for these findings.

	VIT D ng/ml	PTH pg/ml	P1NP ng/ml	BAP µg/L	CTX ng/ml	DKK-1 pmol/L	SCLEROSTIN pmol/L
Patients	23.72 ±9.48	35.92 ±23.48	630.03 ±353.81	72.08 ±38.29	1.52 ±0.45	25.43 ±10.68	24.47 ±9.86
Controls	20.05 ±4.15	20.13 ±7.02	470.22 ±380.24	62.47 ±34.96	1.24 ±0.48	31.48 ±16.51	30.91 ±12.63
p	NS	0.005	NS	NS	0.027	NS	0.03

[Biochemical markers. Data are mean±SD]

P1-d1-286 Bone, Growth Plate and Mineral Metabolism 1

A transient reduction in bone quality in nutrition-induced short-term catch-up growth

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Background: Growth stunting constitutes the most common effect of malnutrition. When the primary cause of malnutrition is resolved, catch-up (CU) growth usually occurs, associated with a dramatic increase in weight and epiphyseal growth plate (EGP) height.
Objective: To check the effect of CU growth on bone parameters.
Methods: The immediate and long term effects of food restriction and CU growth on the structure and mechanical properties of long bones were evaluated by micro-CT scanning and mechanical testing in pre-pubertal rats subjected to 10 days of 40% food restriction (RES group), followed by a renewal of the regular food supply (CU groups). Rats fed ad libitum served as controls (AL).
Results: After 11 day of restriction, rats from the RES group had significantly lower body weight (-48%; $p< 0.05$) and EGP height (-44%; $P< 0.05$). Micro-CT results showed no effect on cortical BMD and BV/TV but a significant reduction in trabecular BV/TV (-48%; $p< 0.05$), concomitant with an increase in Tb. Sp (+90%; $P< 0.05$) and a decrease in Tb. N (-48%; $p< 0.05$). Trabecular BV/TV and Tb. N were significantly greater in the CU group than in the RES (40% and 34% respectively; $p< 0.05$). Mechanical testing showed that food restriction led to weaker and less compliant bones; interestingly, bones of the CU group were also more fragile after one day. However, after a longer period of CU growth (26 days) most of the parameters were corrected. Restriction led to lower IGF-1, leptin and B-ALP levels (by 80%, 99% and 90%, respectively), with an immediate increase during CU.
Conclusions: These results suggest that food restriction in young rats attenuated growth and reduced trabecular bone parameters. While nutrition-induced CU growth led to an immediate increase in EGP height and active bone modeling, it was also associated with a transient and reversible reduction in bone quality. This should be taken into consideration when treating children undergoing CU growth.

P1-d1-287 Bone, Growth Plate and Mineral Metabolism 1

Inverse relationship between vitamin D status and insulin resistance and the risk of impaired fasting glucose in Korean children and adolescents

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Background: Low vitamin D (VitD) status is widespread, and health concerns related to VitD insufficiency/deficiency are increasing. VitD is not only required for bone health but may also play crucial roles in many diseases.
Objective and hypotheses: To investigate whether low vitamin D status was related to insulin resistance (IR) or impaired fasting glucose (IFG) in Korean adolescents, after adjusting for total body fat mass (FM).
Methods: Data from Korea National Health and Nutrition Examination Survey 2009-2010 were analyzed. In total, 1,466 participants (769 males) aged 10-19 years were assessed for serum 25-hydroxyvitamin D [25(OH)D] levels, FM on whole-body dual-energy X-ray absorptiometry, and homeostasis model assessment (HOMA)-IR after an 8-h fast.
Results: Age-, sex-, season-, and physical activity-adjusted regression models showed that serum 25(OH)D levels were significantly related to markers of adiposity [$P = 0.016$ for FM (g), $P = 0.023$ for FM (%), and $P = 0.035$ for FM index]. When the participants were stratified into three 25(OH)D categories [< 15 ($n = 553$), 15 to < 20 ($n = 543$), and ≥ 20 ng/mL ($n = 370$)], significantly decreasing trends for fasting insulin (all $P < 0.001$), HOMA-IR (all $P < 0.001$), and the odds ratios for IFG (all $P < 0.05$) were observed from the lowest to highest 25(OH)D categories, after adjustments for age, sex, physical activity, and all markers of adiposity.
Conclusions: There was a significant inverse relationship between vitamin D status and IR and the risk of IFG, independent of adiposity, in Korean adolescents.

P1-d1-288 Bone, Growth Plate and Mineral Metabolism 1

Effect of β-Estradiol on C-type natriuretic peptide (CNP) induced endochondral ossification in ATDC5 cells

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Background: C-type natriuretic peptide(CNP) has been identified as a new regulator of endochondral bone growth. The murine chondrogenic cell line ATDC5 exhibit the multistep chondrogenic differentiation observed during endochondral bone formation. To date, very little is known about the regulation of CNP signaling components involved in skeletal growth control, with exception of the crosstalk with fibroblast growth factor signaling.
Objective and hypotheses: To investigate the effect of β-Estradiol on CNP-induced endochondral ossification in ATDC5 cells.
Methods: ATDC5 cells were induced differentiation with insulin 10μg/ml(day 0), and studied from day 6. The effects of β-Estradiol on cell proliferation were determined by MTT, while Western-blot were performed to examine the protein levels of CNP, natriuretic peptides receptor B and C(NPR-B, NPR-C) in differentiated ATDC5 cells.
Results: β-Estradiol promoted the proliferation of ATDC5 cells with a time and concentration dependent effect. The maximal effect on cell proliferation occurred at a concentration of 10^{-9}M~10^{-8}M, and at 48h incubation with β-Estradiol at the concentration of 10^{-8}M (compared with the control group, all $P< 0.05$) .
For the protein levels, all of CNP, NPR-B and NPR-C increased from the concentration of 10^{-11} M β-Estradiol, CNP and NPR-B peaked in a concentration of 10^{-10}M ($P< 0.05$), while NPR-C peaked in a concentration of 10^{-9}M ($P< 0.05$). At 10^{-8}M, β-Estradiol promoted CNP synthesis and peaked at 24h. Meanwhile, β-Estradiol[10^{-8}M] seemed to increase NPR-B and NPR-C level at 24h but inhibited NPR-B and NPR-C synthesis at 72h and 96h (compared with the control group, all $P< 0.05$).
Conclusions: β-Estradiol promotes the cell proliferation, significantly increases the protein expressions of CNP, and that of NPR-B and NPR-C in ATDC5 cells to some extent. Estrogen may be one of the regulators of CNP signaling pathway, facilitating CNP induced endochondral ossification (long bone growth).

P1-d1-289 Bone, Growth Plate and Mineral Metabolism 1

Hereditary 1,25-dihydroxyvitamin D-resistant rickets with homozygous *VDR* mutation - an extremely rare case of maternal uniparental disomy of chromosome 12 detected by genome-wide SNP array

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Introduction: Hereditary 1,25-dihydroxyvitamin D-resistant rickets (HVDRR) is an autosomal-recessive genetic disease caused by biallelic mutations in the vitamin D receptor (*VDR*) gene located on chromosome 12q13.11.
Some recessive disorders have been reported to be caused by uniparental disomy(UPD) of a single parent allele with mutation, but have not reported in HVDRR. Moreover, complete isodisomy of chromosome 12 is extremely rare.
Objective: To determine the pathogenesis of non-Mendelian inheritance of a HVDRR patient with homozygous *VDR* mutation by genome-wide SNP array.

Subject and methods: A 2 year-old-girl with short stature (-2.5 SD), alopecia and gait instability showed rickets pattern in X-ray exams. Her lab tests showed serum Ca 7.7 mg/dl, iP 3.0 mg/dl, ALP 8,891 IU/l, iPTH 576 pg/ml, $1,25(OH)_2D$ 137 pg/ml, 25(OH)D 20.1 ng/ml. There is no parental consanguinity in this case and no familial history of rickets. We diagnosed her as a HVDRR and prescribed high dose of calcium and alfacalcidol.
All coding exons of *VDR* gene were sequenced and whole-genome SNP array were performed in the patient and the parents with informed consent.
Results: Sequencing of the *VDR* gene revealed that the patient has homozygous mutation of R73X, a premature nonsense mutation reported to result in loss-of-function of VDR. The mutation was detected in her mother heterozygously, but not in her father. Whole-genome SNP array revealed that this case has complete isodisomy of chromosome 12 derived from the mother.
Conclusion: SNP array was useful in the detection of UPD. HVDRR in this case was caused by a rare maternal UPD of the complete chromosome 12 with *VDR* mutation. The fact that the patient shows no symptoms but rickets in this case, suggests that there are no diseases caused by genomic imprinting in chromosome 12.

P1-d1-290 Bone, Growth Plate and Mineral Metabolism 1

Mouse polycomb regulates infantile long bone growth and development

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Background: Polycomb Group (PcG) proteins tether at the specific chromatin target sites, and regulate expression of target gene. PcG genes commonly regulate *Hox* gene clusters, whereas each member of PcG proteins regulates its distinct targets during fetal development. One of the members of PcG genes, *Cbx2*, specifically controls gonadal and adrenal development through the regulation of key transcriptional factor genes, such as *Nr5a1 (Ad4bp/Sf-1)* and *Lxh9*. By contrast, postnatal functions of *Cbx2* are largely unknown.
Objective and hypotheses: *Cbx2* KO newborn mice were normal in body size. However, they exhibited progressive growth retardation and more than half of them died by weaning stage. Because of the small body size of *Cbx2* KO infant (~ 4-week-old) mice, critical functions of *Cbx2* in bone elongation were predicted. To elucidate the function of *Cbx2* in long bone growth, we investigated the cartridge and trabecular of long bone metaphysis in *Cbx2* KO infant mice.
Methods: Phenotypic analyses of femurs and tibiae in 4-week-old *Cbx2* KO mice were performed by histological analyses (HE, ALP, TRAP staining), and micro computed tomographic measurement in comparison with wild type littermate. The number of mesenchymal progenitor cells was assessed by colony-formation units (CFU-fap) assays.
Results: Bone volumes of distal femur trabecular were significantly lower and the numbers of osteoblast lineage cells were reduced in *Cbx2* KO relative to wild type mice. In contrast, the numbers of osteoclast cells in the metaphysis was unaltered in *Cbx2* KO mice. Furthermore cartilaginous growth plates were disorganized and thinner *Cbx2* KO mice in comparison with those of wild type littermate.
Conclusions: Mouse PcG gene *Cbx2* regulates chondrocyte progression and osteoblast development during infancy.

P1-d1-291 Bone, Growth Plate and Mineral Metabolism 1

Nutritional rickets: vitamin D, calcium or the genetic make up?

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Introduction: The role of *VDR* genotypes in predisposition, modification of severity and response to therapy in rickets and the roles of vitamin D and Ca as therapies were analyzed.
Subjects and methods: 109 infants (7 m-3 y) with active rickets were assigned to 3 treatment groups based on dietary Ca intake: those deficient were assigned to two groups: (Group 1: if > 2 h/w of sun exposure, received Ca supplementation for 6 m; Group 2: if < 2 h/w of sun exposure, received vitamin D3 600,000 IU IM plus Ca supplementation for 6 m); Group 3: normal dietary Ca intake; received 600,000 IU D3 IM plus 40 mg elemental Ca/kg/day (if under 1 y) and 50 mg/kg/day (if over 1 y) for 2 weeks.
Serum Ca, P, ALP, 25-OH-D, 1,25-OH-D and PTH were measured at enrolment, every month and at radiologic healing. Radiographs of wrists and knees were scored with a 10-point system. DNA was taken to genotype 28 *VDR* SNPs.
30 healthy children served as controls.
Results: *VDR* SNP genotypes were associated with baseline Ca (6 SNPs), PTH (3), X-ray score (3) and 1,25-OH-D (1). Combined genotypes at 8 SNPs showed associations with baseline Ca (r^2=0.34; p=0.0009), 25-OH-D (r^2=0.21; p=0.02) and 1,25-OH.D (r^2=0.28; p=0.004). *VDR* SNP genotype frequency comparison in the 3 patient groups revealed increased frequencies of major allele homozygous genotypes at rs7305032 and rs2525044 in Group 1 compared to Groups 2 and 3 and controls. *VDR* genotypes did not associate with response to therapy regimens in terms of time to healing.
Conclusions: We found an association between rickets severity and *VDR* genotypes as judged by bone score, Ca, PTH, 25-OH-D and 1,25-OH-D.
VDR genotypes at rs7305032 and rs2525044 may predispose to rickets when Ca intake is low and sun exposure and 25-OH-D are normal. *VDR* genotypes were not associated with response to therapy.
A history of calcium intake and sun exposure could be used for management planning as healing occurred at about the same time in the 3 groups.

P1-d1-292 Bone, Growth Plate and Mineral Metabolism 1

Children and adolescents with cystic fibrosis have normal volumetric BMD and geometry at the radius, but low muscle area at the forearm

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Background: While studies in adults with cystic fibrosis (CF) showed increased fracture risk and decreased bone mineral density (BMD), the results of the pediatric studies have been contradictory.
Objective and hypotheses: Our aimes were to assess volumetric BMD, bone geometry and muscle area at the forearm in children with CF using peripheral quantitative CT (pQCT). We hypothesized that bone geometry parameters will correlate with pulmonary function.
Patients and methods: Fifty-three patients with CF (median age 12.9 yrs, range 6.7-18.8, 29 girls) were examined by pQCT at the non-dominant forearm. Median forced expiratory volume in one second (FEV1, % predicted) of the spirometry examinations performed during the last year before densitometry was selected as a surrogate of pulmonary function. The differences from reference data were tested by one-sample T test, Pearson correlation coefficient was used to correlate pQCT-derived bone parameters with FEV1.
Results: Trabecular BMD was normal (mean Z-score -0.2±1.3, n.s.) in children with CF. Total bone cross-sectional area, cortical bone area and cortical thickness were all normal when adjusted for height (mean Z-scores 0.0±1.1, 0.0±1.0 and 0.0±0.8, respectively). Cortical BMD was increased (mean Z-score 1.0±0.9, $p< 0.001$). As a consequence of decreased muscle area (MA, mean Z-score -1.5±1.5, $p< 0.001$) the bone mineral content to MA ratio was increased (mean Z-score 1.3±1.0, $p< 0.001$). Whereas FEV1 was positively correlated to muscle area (R^2=0.20, $p< 0.002$) and bone geometry ((i.e. cortical thickness (R^2=0.24, $p< 0.001$) and cortical bone area (R^2=0.20, $p< 0.002$)), the correlation with BMD was weak (R^2=0.08, p=0.035 and R^2=0.007, n.s. for trabecular and cortical BMD, respectively).
Conclusions: Children and adolescents with CF have adequate bone density and geometry at the radius but decreased muscle mass at the forearm. FEV1 seems to be a good predictor of changes in muscle area and bone geometry in these patients.

P1-d1-293 Bone, Growth Plate and Mineral Metabolism 1

Ex vivo model reveals an important role for PDGFR-β in development of fetal mouse metacarpal growth plate

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Background: Platelet-derived growth factor (PDGF) ligands act as mitogens for both hematopoietic and mesenchymal bone progenitor cells, and migration and proliferation of these cells is stimulated by different PDGF isoforms. Non-resorbing osteoclasts induce osteoblast migration and differentiation mainly through PDGFR-β signaling which in turn maintains osteoblast survival. However, even though the importance of PDGFR-β is well established in bone cells, surprisingly little is known about its role during early bone development.
Objective and hypotheses: The aim of our study was to investigate the role of PDGFR-β in early bone development by inhibiting its actions by a specific inhibitor in an ex vivo metacarpal bone culture where the entire developing long bone is present with its original cell types.
Methods: Metacarpal bones of mouse embryos (E14.5 to E18.5) were cultured for six days in control medium or in medium supplemented with PDGFR-β-specific inhibitor (D-64406; Calbiochem). Structural changes were analyzed microscopically. Uncultured bones were investigated for gene expression. In addition, effects of PDGFR-β inhibition on osteoblast proliferation and differentiation were separately investigated in CD73+ rat cells.
Results: In osteoblast cell culture, PDGFR-β inhibition resulted in reduced proliferation rate. However, the ability to produce alkaline phosphatase protein was un-affected by the inhibition. In uncultured metacarpal bones PDGFR-β was highly expressed from embryonic day E14.5 to E20.5. Histomorphological evaluation of the bones cultured under PDGFR-β inhibition resulted in dysorganization of the growth site. There was hardly any proliferating zone and the site was ectopically populated with hypertrophic chondrocytes with flattened morphology.
Conclusions: Our results clearly indicate that the regulation of PDGFR-β signaling is highly important for organization of growth plate during early bone development.

P1-d2-294 Bone, Growth Plate and Mineral Metabolism 2

Bone disease in children with geroderma osteodysplasticum (GO): a 25-year experience from a single tertiary centre

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Background: Geroderma Osteodysplasticum (GO) is a rare autosomal recessive connective tissue disorder characterised by progeria like facies, wrinkled lax skin and propensity to fragility fractures. There have been very few reports in literature describing skeletal manifestations of GO and its management.
Objective and hypotheses: To describe the spectrum of skeletal manifestations that can range from no bony involvement to severe vertebral and long bone fractures requiring treatment with bisphosphonates in children with GO.
Methods: Retrospective case note analysis of five patients (3 female; 2 male) diagnosed with GO and referred to our Paediatric metabolic bone service in the last 25 years.
Results: All five children were born to consanguineous parents of Pakistani origin. Four out of 5 patients had significant bone problems at presentation or developed them subsequently. Two patients had congenital dislocation of hips and two had talipes equinovarus. Four patients with radiologically apparent osteopaenia developed vertebral wedge fractures. Three children suffered non-vertebral fractures which included: the femur, the tibia, the clavicle, a metatarsal bone and a middle phalanx. Trans-iliac bone biopsies in 2 children showed severe cortical and trabecular osteopaenia. Data on bone densitometry, which was performed in 3 children, is shown in the table below.

Patient no	Age (yrs)	Lumbar Spine bone mineral apparent density Z score (g/ml3)	Lumbar Spine volumetric trabecular BMD Z score (mg/ml3)	Distal radial total BMD Z score (mg/ml3)	Distal radial trabecular BMD Z score (mg/ml3)
1	5	0.169	-1.62	1.3	0.29
1	11	-3.736	-5.16	-0.03	-2.03
3	5.4	0.498	-1.98	-2.35	-1.6

Cyclical intravenous Pamidronate therapy resulted in reduced long-bone fractures, remodelling of vertebral fractures and improvement in bone mineral density (BMD) values at axial and appedicular skeletal sites.
Conclusions: In our experience, severity of bone disease in GO is variable. It is characterised by cortical and trabecular osteopenia and Pamidronate therapy appears to improve BMD and reduce the fracture risk.

P1-d2-295 Bone, Growth Plate and Mineral Metabolism 2

Hereditary 1,25-dihydroxyvitamin D-resistant rickets (HVDRR) inherited as a dominant trait caused by a novel vitamin D receptor mutation with dominant negative effect

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Background: HVDRR is a rare disease caused by mutations in the *VDR* gene. It is usually transmitted by autosomal recessive trait, by loss-of-function mutations.
Objective: HVDRR may be occasionally inherited as a dominant trait in case of a dominant-negative mutation.
Subjects and methods: An 18-month-old Japanese boy was evaluated for short stature and bow-legs. His father had been treated for rickets for a short period during childhood, and his paternal grandfather had bow-legs. We diagnosed him as HVDRR per his laboratory data (calcium 8.9 mg/dl, phosphate 3.3 mg/dl, ALP 3,346 IU/l, iPTH 480 pg/ml, 25(OH)D 20 ng/ml, and 1,25(OH)2D 304 pg/ml) and radiographic finding of rickets.He was successfully treated by alfacalcidol which could be stopped later. Sequence analyses of the *VDR* gene were performed and the functional consequences of the detected mutations were analyzed for transcriptional activity, ligand binding, and interaction with RXR and cofactors.
Results: A novel compound heterozygous mutation (Q400LfsX7 and R370H) was identified in the patient. Q400LfsX7 was detected in his father heterozygously, and R370H in his healthy mother. Functional studies revealed that transcriptional activity of Q400LfsX7-VDR was markedly disturbed. The mutant had a dominant-negative effect on wild-type VDR. Ligand binding affinity of Q400LfsX7-VDR was totally impaired. Interestingly, Q400LfsX7-VDR had a strong interaction with co-repressor NCoR even in the presence of the ligand. In contrast, R370H-VDR revealed to be functionally similar to the wild-type, indicating that this may be a rare variant.
Discussions: We found a dominant negative mutant of VDR causing dominant inherited HVDRR. Transcriptional repression may be due to its ligand-independent interaction with a co-repressor. The phenotype was less severe for HVDRR and some cases may be misdiagnosed as vitamin D deficiency. Our finding together with another reported pedigree provides a distinct inheritance of HVDRR.

P1-d2-296 Bone, Growth Plate and Mineral Metabolism 2

FGF23 is modulated by calcium in children under peritoneal dialysis

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Background: Chronic Renal Failure (CRF) is associated to severe mineral metabolism disturbances. New molecular markers have been introduced in the evaluation of these complications. Fibroblast Growth Factor23 (FGF23) causes renal phosphaturia and suppresses renal production of 1,25 (OH)2 vitamin D in health and uremic patients.
Objective: The aim of this study was to characterize the FGF23/Klotho axis in children under peritoneal dialysis (PD), and study its associations with mineral imbalance.
Methods: We studied stable patients with more than 3 months on PD. without vitamin D levels < 20 pg/ml or active nephrotic syndrome condition. Anthropomorphic, dialytic and biochemical measurements were obtained at the 2nd month of the study. Human intact FGF-23 levels (pg/ml) by a 2-site ELISA kit; Klotho cofactor by a solid phase sandwich ELISA kit (pg/ml). Descriptive statistics, univariate and multivariate analysis were performed.
Results: 38 patients, 20 males, age 1-15 y.o. Time on DP 11±10 months (3-36). Height/age Z value -1.89±1.17 and nPNA was 1.01±0.31; Residual and total dialysis dose (Kt/V) were 1.2±1.5 and 2.8±1.1 respectively. Serum calcium and phosphorus were 9.9±1 and 5.46+1 mg/dl, and PTH mean value 354+277 pg/ml. Mean Vitamin D (25OHD3) plasma level was 34+6.6 mg/dl. FGF23 and Klotho values were 222+314 and 138+57 pg/ml respectively. No correlation was found between these 2 variables. Univariate analysis showed a significant negative correlation between FGF23 vs height/age Z value and residual Kt/V, and a positive correlation with serum calcium. No correlation was found between FGF23 Log vs serum phosphorus, vitamin D and PTH. The multivariate analysis showed that the main variable explaining FGF23 Log change was serum calcium (r2 0.63, p< 0.001).
Conclusions: The increase in calcium produces a concomitant increase in FGF23 plasma levels. Our results suggest that calcium is the main variable affecting FGF23 levels in dialyzed children.

P1-d2-297 Bone, Growth Plate and Mineral Metabolism 2

Altered bone geometry, strength and quality in children born SGA at term and in children born AGA and SGA prematurely

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Background: Prematurity and low birth weight for gestational age (SGA) are both associated with a decrease in bone mass.
Objective and hypotheses: The aim of the study was to investigate bone geometry, strength and quality in 3 different groups of children: term SGA, premature AGA (prem AGA) and premature SGA (prem SGA).
Methods: 88 patients (45 f, 43 m), mean age 11.3 years, height SDS 0.09±0.27 and BMI SDS -0.44±0.68; 16 were term SGA, 23 prem SGA and 49 prem AGA. Bone geometry was evaluated from digitalized X-rays taken at the level of the 2nd metacarpal bone. The following parameters were assessed: outer (D) and inner (d) diameter, cortical area (CA), medullary area (MA), metacarpal index (MI), cross sectional area (CSA) and bending breaking resistance index (BBRI). Bone quality was evaluated by ultrasound, measuring the amplitude dependent speed of sound (AdSos) and bone transmission time (BTT).
Results: term SGA showed significantly lower values of D (p< 0.005), d (p< 0.025), MA (p< 0.0005), CA (p< 0.0005), CSA (< 0.0005), BBRI (p< 0.0005) and AdSos SDS (p< 0.05). Prem SGA showed lower values of D (p< 0.0005), d (p< 0.0005), MA (p< 0.0005), CA (p< 0.0005), CSA (p< 0.0005), BBRI (p< 0.0005) and BTT SDS -0,91±0,89 (p< 0.0005). Prem AGA had D (p< 0.0005), d (p< 0.0005), MI (p< 0.05), MA (p< 0.0005), CA (p< 0.0005), CSA (p< 0.0005), BBRI (p< 0.0005) and BTT SDS (p< 0.0005) also significantly lower. By ANOVA, the three groups were not different, apart from the BTT SDS which was significantly reduced in the group of premature SGA.

	D sds	d sds	MI sds	MA sds	CA sds	CSA sds	BBRI sds	Ad-Sos sds	BTT sds
AGA n=49	-1,2 ±1,1*	-0,7 ±0,9*	0,3 ±1,1*	-0,8 ±0,8*	-0,9 ±0,8*	-4,3 ±3,5*	-3,8 ±2,9*	0,1 ±1,2	-0,5 ±1,0*
SGA prem n=23	-1,4 ±1,1*	-0,8 ±0,8*	0,2 ±0,8	-0,8 ±0,7*	-1,2 ±0,7*	-5,6 ±3,6*	-4,9 ±2,3*	-0,1 ±1,1	-0,9 ±0,9§*
SGA term n=16	-1,3 ±0,7*	-0,9 ±0,8*	0,3 ±0,9	-0,8 ±0,7*	-1,1 ±0,6*	-4,5 ±2,0*	-4,2 ±1,8*	0,5 ±1,2*	-0,1 ±0,7§

[Table 1_ Bone geometry, strength and quality.]

Conclusions: Children born prematurely (AGA and SGA) and at term (SGA) seem to have smaller and weaker bones. In particular, children born small for gestational age prematurely, seem to be the most affected.

P1-d2-298 Bone, Growth Plate and Mineral Metabolism 2

Cardiovascular involvement in children with osteogenesis imperfecta

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Background: Osteogenesis imperfecta is a hereditary disease resulting from mutation in type I procollagen genes. One of the extra skeletal manifestations of this disease is cardiac involvement. The prevalence of cardiac involvement is still unknown in the children with osteogenesis imperfecta, therefore, the present study aimed to investigate the prevalence of cardiovascular abnormalities in such patients.
Materials and methods: 24 children with osteogenesis imperfecta and 24 normal children who were matched with the patients regarding sex and age were studied. In both groups, standard echocardiography was performed, heart valves were investigated. Dimensions of left ventricle, aorta annulus, sinotubular junction, ascending and descending aorta were measured and compared between the two groups.
Results: The results revealed no significant difference between the two groups regarding age, sex, ejection fraction, shortening fraction, mean of aorta annulus, sinotubular junction, ascending and descending aorta, but after correction based on the body surface area, dimensions of aorta annulus, sinotubular junction, ascending and descending aorta in the patients were significantly higher than the control group (P< 0.05). 2 patients (8.3%) had aortic insufficiency and 5 patients (20%) had tricuspid regurgitation, 3 of whom had gradient>25 mm Hg and 1 patient had pulmonary insufficiency with indirect evidence of pulmonary hypertension.
Conclusion: The prevalence of valvular heart diseases was higher in children with osteogenesis imperfecta . Furthermore, based on the body surface area, the parameters of aorta annulus, sinotubular junction, ascending and descending aorta were higher among the patients. In conclusion, cardiovascular investigation is recommended in these children.

P1-d2-299 Bone, Growth Plate and Mineral Metabolism 2

The evaluation of vitamin D supplementation dose during pregnancy in a high-risk population

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Background: Maternal vitamin D deficiency is primary risk factor for neonatal vitamin D deficiency, however the debate about vitamin D supplementation dose during pregnancy still continues.
Objective: To compare the doses of 600 IU/day (recommended by international societies), 1200 IU/day (recommended in our national program), 2000 IU/day (suggested by some researchers).
Methods: Study group was consisted of the pregnant women admitted to Kocaeli Maternity and Child hospital between May-2011 and May 2012. The mean age of study group was 27.3 ±5.1years, mean gestational age was 8.9±2.4 weeks. Initial serum 25OHD levels of study group were measured and subjects divided into 3 groups randomly. 600, 1200 and 2000 IU/day vitamin D was supplemented to the 1st group (control group, n:31), 2nd group (n:31) and 3rd group (n:32), respectively. Serum calcium, 25OHD, calcium/creatinine ratio in spot urine samples of the subjects were measured in the follow-up period. Serum calcium and 25OHD levels of their infants were measured as well.
Results: Socio-demographic characteristics of the subjects are given in Table 1. The mean initial 25OHD level of study group was 10.4 ±3.4 ng/ml,only 2% of them had sufficient vitamin D status (≥20 ng/ml). The ratio of the subjects who had sufficient 25OHD post-supplementation was 80% in the 3rd group,it was significantly higher than the 1st and 2nd groups (the ratio was 42% and 39%, respectively) (p:0.03). Similarly the ratio of the infants who had sufficient vitamin D levels was 91% in the 3rd group and it was significantly higher than the 1st and 2nd groups (the ratio was 36% and 52%, respectively) (p:0.006). None of the subjects did not have hypercalcemia or hypercalciuria.

	N:91
Age (year)	27.3 ±5.1 (16.2-42.2 median 26,6)
Gestational age (week)	8.9±2.4 (8-14)
Clothing style	West type 12% (n= 11) Covered 88% (n =80)
Education level	illiterate: 2.2% (n =2) primary school: 67% (n =61) high school 22% (n =20) college: 8.8% (n =8)
Settlement	Urban 68% (n =62) Rural 32% (n =29)
Level of income (TL/month)	1435±866 (600-5000, median 1200)
Exposure to sun (hour/day)	None: 25% (n =23) 1-2 hours: 57% (n =52) 3-5 hours: 18% (n= 16)

[The socio-demographic characteristics of subjects]

Conclusions: At least 2000 IU/day vitamin D is needed to ensure adequate vitamin D status in pregnancy and early infancy, particularly in the high-risk populations.

P1-d2-300 Bone, Growth Plate and Mineral Metabolism 2

Fibroblast growth factor-23 (FGF-23) and matrix extracellular phosphoglycoprotein (MEPE) levels in healthy children and pregnant and lactating women, and their roles in phosphate metabolism

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Background: FGF-23 and MEPE are the phosphaturic factors which cause renal phosphate wasting.
Objective and hypotheses: We hypothesized that serum FGF-23 and MEPE levels show variation with age, gender and pregnancy or lactation in women and these physiological changes could be explanatory for variable age of presentation in autosomal dominant hypophosphatemia. We aimed to study age and gender specific reference values and changes during pregnancy and lactation in MEPE and FGF-23 levels and to identify their regulatory factors.
Methods: 96 healthy children (50F) and 31 young women (11 healthy, 10 pregnant, 10 lactating). Serum (S) and urine (U) levels of Ca, PO_4 and Cre and, ferritin, PTH, 25OH vitD, ALP, IGF-I and IGFBP-3 were determined. FGF-23 (Milipore) and MEPE (Uscn Life Science Inc) concentrations were measured bye using ELISA. Renal reabsorption of PO_4 (TRP) and renal PO_4 threshold ($TMPO_4$/GFR) and z-scores for each data were calculated.
Results: The FGF-23 concentrations showed no difference between age groups. MEPE concentrations decreased with age and over age 7 were similar to adult levels (Fig). The highest MEPE concentration was observed in pregnant women (6,5±6.65 vs 1.5±1.2 ng/ml in healthy women, p:0.026). FGF-23 z-score was positively correlated with MEPE (r:0.22, p:0.01), S-PO_4 (r:0.18, p:0.05) and $TmPO_4$/GFR (r:0.21, p:0.02) z-scores. S-PO_4 z-score was positively correlated with U-PO_4/Cre ratio z-score (r:0.24, p:0.02). MEPE was positively correlated with TRP (r:0.22, p:0.02) and $TmPO_4$/GFR (r:0.19, p:0.04) z-scores. Ferritin was not correlated with any of the parameters except PTH (r:-0.19, p:0.04).
Conclusions: In physiologic conditions, increase in S-PO_4 increases FGF-23 and U-PO_4 excretion, however, contrary to pathological conditions, FGF-23 and MEPE more seem to increase U-PO_4 reabsorption. The elevation in MEPE levels during pregnancy needs to be investigated further.

P1-d2-301 Bone, Growth Plate and Mineral Metabolism 2

Microcephaly, multiple dysmorfisms and diabetes mellitus: multiple genetic involvement

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Introduction: Autosomal recessive primary microcephaly (MCPH) is a rare disorder of neurogenic mitosis characterized by reduced head circumference at birth with variable degree of mental retardation. This heterogeneous condition can be associated with severe cerebral malformations including polymicrogyria, schizencefaly, lissencephaly, pachygyria and cerebellar hypoplasia. Recent studies showed that WDR62 is one of the genes involved in MCPH. No cases of microcephaly with polymicrogyria due to WDR62 mutation associated with childhood-onset diabetes mellitus have been described so far.
Case report: We report a female of tunisian origin, daughter of consanguineous parents, affected by primary microcephaly and mental disability who developed diabetes ketoacidosis at the age of 5.7 years. Family history was positive for gestational diabetes (mother). Clinical features included severe microcephaly (head circumference 44.5 cm), receding forehead, eyelashes and thick eyebrows, drooling, many destructive caries in the oral cavity, low-set thumbs, broad toes. Height was at 50th percentile, weight was at the 10th percentile. β-cells autoantibodies were negative. Baseline C peptide was 0,2 ng/mL. Screening for autoimmune thyroiditis and celiac disease was negative. Karyotype was normal. During follow-up she showed partial remission and good metabolic control with insulin requirement < 0,5 U/Kg following diabetes diagnosis. Cerebral MRI showed symmetrical perisylvian polymicrogyria with extension to the temporal, frontal and parietal lobes. Based on clinical features genetic analysis for WDR62 was performed by direct sequencing. Molecular sequencing revealed a homozygous pattern for the missense change c.2588G>A, p.Arg863His (exon 22) in the WDR62 gene. This mutation has never been described.
Conclusions: This case showed a novel homozygous WDR62 mutation in a girl with primary microcephaly, mental disability and then DKA and enlarge the spectrum of WDR62 variants.

P1-d2-302 Bone, Growth Plate and Mineral Metabolism 2

The role of growth hormone in enchondroplasia and chondral osteogenesis: evaluation by hand x-ray

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Background: The process of growth and maturation of the long bones (Radius Ulna) and short bones (phalanges and metacarpals) of the hand (enchondroplasia) differs from the carpal cuboid bones (chondral osteogenesis).
Objective and hypotheses: We aimed to determine role of GH in the skeletal maturation process.
Methods: Bone age (BA) x-ray was performed according to Greulich and Pyle, and was expressed for short bones, long bones and carpals as years ('y') of delay relative to chronological age in 37 children with GHD age 7.9±1.9 (m±sd), and in 73 ISS children, age 7.57 ±2.0, during 2 years of GH treatment.
Results: At start bone maturation in ISS children was mostly delayed for the carpals (3.1±1.1 'y') as compared with 2.36±1.30 and 1.17±1.1 'y' for long ($p< 0.0001$) and short bones ($p< 0.0001$), respectively. In GHD, maturation was delayed 3.48±1.4 'y' for the carpals , 2.86±1.5'y' for long bones (n.s) and 1.76±1.1 'y' for short bones ($p< 0.0001$). After 2 years of GH treatment, long bones had advanced by 3.33±1.4 'y' in ISS and 3.26±1.1 'y' in GHD, short bones advanced by a mean 1.93±0.7 'y' in ISS and 1.87±0.6 in GHD , and carpal bones by 4.22±1.3 'y' in ISS and 4.12±1.1 'y' in GHD (figure 1). Long bones and carpal bones advanced significantly ($p< 0.0001$) in both ISS and GHD during 2 years of treatment, but short bones did not.
Conclusions:
1. GH therapy accelerates mostly carpal bones (surrogates for the vertebrae), implying that
2. The dominant physiological effect of GH is on chondral osteogenesis with a milder effect on enchondroplasia.
3. A BA profile with mostly delayed carpals is typical for GHD.
4. BA reading must include the carpal bones.

P1-d2-303 Bone, Growth Plate and Mineral Metabolism 2

Bone microarchitecture and vertebral bone marrow adiposity in young women with childhood-onset type 1 diabetes mellitus (T1DM)

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Background: Adults with T1DM have an elevated fracture risk but conventional measures of bone density assessment do not show a clear abnormality.
Objective and hypotheses: To study trabecular bone microarchitecture and vertebral marrow adiposity in young women with childhood-onset T1DM.
Methods: 13 women with T1DM with a median age at diagnosis of 9.3yrs (0.75,14.2) and 13 healthy women (Ctrl) were scanned by a 3-TMRI to obtain images of trabecular bone of proximal tibia at a median age of 24yrs (17,35) and 23yrs (19,37), respectively. Apparent measures of bone volume/total volume (appBV/TV), trabecular thickness (appTb.Th),number (appTb.N) and separation (appTb.Sp) were measured. MR spectroscopy of the L3 was also performed to quantify vertebral bone marrow adiposity (VBMA).
Results: Median appTb.Th in T1DM and Ctrl groups were similar at 1.10 (0.9,1.49) and 1.11 (0.96,1.37), respectively. Median AppBV/TV in the T1DM was lower than in Ctrl at 0.29 (0.25,0.31) and 0.32 (0.26,0.37), respectively ($p=0.03$). Median appTbN in T1DM was also lower than in Ctrl at 0.25 (0.20,0.27) and 0.29 (0.23,0.30), respectively ($p=0.009$). In addition, median appTb.Sp in T1DM was higher than Ctrl at 2.72 (2.24-3.38) and 2.30 (2.09-2.97), respectively ($p=0.03$). In T1DM, appTb.N and appBV/TV showed a negative association with age (r,-0.6,$p=0.05$). Also appTb.N showed a positive association with age at diagnosis (r,0.7,$p=0.02$) and negatively with disease duration, (r,-0.6,$p=0.03$). The 2-year mean HBA1c for the T1DM group was 8.3% (6.18,9.36) and showed a negative association with the appTb.Th (r,0.7;$p=0.009$). Although VBMA was similar in the two groups, in T1DM, it showed a negative association with appTb.N (r,-0.7,$p=0.009$), and a positive association with disease duration (r,0.8;$p=0.002$).
Conclusions: Young women with childhood-onset T1DM have altered bone microarchitecture which may be related to bone marrow adiposity. The use of MR for studying conditions that are associated with a fracture risk needs further exploration.

P1-d2-304 Bone, Growth Plate and Mineral Metabolism 2

25-Hydroxyvitamin D (25OHD), osteocalcin (OC), under-carboxylated osteocalcin (uOC) and N-terminal propeptide of type 1 procollagen (P1NP) in prepubertal and pubertal survivors of childhood cancer compared with healthy controls

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Background: We have reported relative hyperinsulinemia (HI) in prepubertal survivors of childhood cancer and HI/abnormal glucose tolerance (aGT) in 23% pubertal survivors. Reports of 25OHD deficiency in survivors and that OC & uOC may be linked to insulin sensitivity led us to explore this in our study population.
Objectives:
1) Is 25OHD deficiency increased in survivors?
2) Are bone formation markers (BFM) different in survivors vs controls?
3) Do OC ± uOC correlate with insulin sensitivity independent of other BFM (P1NP)?
Methods: 25OHD, OC, uOC & PINP in 109 survivors (5-17yrs, 34 prepubertal), median 8.9yrs [2.3-17.4] from diagnosis, were compared with 132 controls (5-17yrs, 65 prepubertal), adjusted for gender and Tanner pubertal staging (II-IV vs V). Relationships with HI/aGT, BMI & waist:height (W:H) ratio were sought.
Results:

	25OHD nmol/L	OC ng/mL	uOC ng/mL	P1NP ng/mL
		Prepubertal		
Survivors	64.8±17.5	96.9±31.1	40.7±27.4	575±287
Controls	73.1±23.2	78.3±23.2	28.6±16.1	483±121
Difference (CI95%)	-6.5 (-15.6-2.6)	+18.5 (7.5-29.5) p=0.001	+12.1 (3.4-20.8) p=0.007	+92.5 (10.9-174.1) p=0.03
		Pubertal		
Survivors	64.1±23.4	76.1±47.2	30.9±31.9	414±339
Controls	59.9±20.5	97.4±43.3	42.4±28.7	558±327
Difference (CI95%)	+3.5 (-3.8-10.8)	-18.8 (-32.0--5.6) p=0.006	-10.0 (-19.5--0.6) p=0.04	-124.7 (-215.5--33.9) p=0.007

[Table 1]

Survivors and controls had similar rates of 25OHD deficiency (< 50nmol/l; 24.8% vs 20.5%). BFM were higher in prepubertal but lower in pubertal survivors versus controls. There was a trend to lower OC and P1NP in pubertal survivors with HI/aGT ($p\leq0.09$). On linear regression, OC, P1NP & 25OHD were lower in both pubertal survivors and controls with W:H ratio >0.5 with no independent relationship with BMI ($p\leq0.004$).
Conclusions: 25OHD levels are similar, but BFM are different in survivors

and controls and do not show the expected rise during puberty in survivors. Changes in OC and uOC are not independent of P1NP and appear to be more dependent on abdominal adiposity than insulin sensitivity.

P1-d2-305 Bone, Growth Plate and Mineral Metabolism 2

Autosomal recessive hypophosphatemic rickets type 2 (ARHR2) and hypertension due to novel compound heterozygous mutations within the *ENPP1* gene

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Background: Hypophosphatemic rickets is a heterogeneous group of renal phosphate wasting disorders caused by elevated circulating fibroblast growth factor 23 (FGF23) which inhibits phosphate reabsorption and 1,25-dihydroxyvitamin D synthesis in the proximal renal tubules. Mutations in any of the five known genes - *PHEX* (XLH [MIM 307800]), *FGF23* (ADHR [MIM 193100]), *SLC34A3* (HHRH [MIM 241530], *DMP1* (ARHR1[MIM 241520]), and *ENPP1* (ARHR2 [MIM 613312]) causes hypophosphatemia.
Objective and hypotheses: We report a 13 years old boy with a late onset of rickets, who presented with progressive bone deformity, genu valgus and bone pain since the beginning of puberty. In addition the patient had bilateral conductive hearing deficit and hypertension. Hypertension was related to hyperreninemia following stenosis of the right renal artery due to myointimal proliferation.
Methods: Biochemical investigations showed an elevated alkaline phosphatase activity, decreased serum phosphate levels and an elevated FGF23 level. Autosomal dominant hypophosphatemia was excluded by sequence analysis of the *FGF23* gene. Due to the complex phenotype sequencing of the *ENPP1* (ectonucleotide pyrophosphatase/phosphodiesterase 1) gene was performed.
Results: Sequence analysis of *ENPP1* revealed one heterozygous non-synonymous single nucleotide variation (SNV) in exon 2 (NM_006208.2:c.275G>A, NP_006199.2:p.Gly92Asp) and one heterozygous splice site mutation in intron 21 (NM_006208.2:c.2230+1G>A) of the *ENPP1* gene. Both SNVs were not found in databases of sequence variations (dbSNP137) and of mutations (HGMD), and within 1846 in house exomes.
Conclusion: We identified two novel compound heterozygous mutations within the *ENPP1* gene in a boy with autosomal recessive hypophospatemia and a concomitant mild phenotype of generalized arterial calcification of infancy.

P1-d2-306 Bone, Growth Plate and Mineral Metabolism 2

Hip structural analysis in adolescent boys with anorexia nervosa and controls

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Background: We have reported lower bone mineral density (BMD) at the hip in adolescent boys with anorexia nervosa (AN) compared with controls. Although studies have described bone structure and geometry in girls with AN, these data are not available for boys with AN. Hip structural analysis (HSA) using dual energy x-ray absorptiometry (DXA) is a validated technique to assess hip geometry and strength, while avoiding the radiation associated with quantitative CT.
Objective and hypotheses: We hypothesized that boys with AN compared with controls would have impaired hip structure and geometry (as assessed using HSA).
Methods: We enrolled 15 boys with AN and 16 normal-weight controls between 12-19 years old, and used DXA to assess hip BMD, body composition and for HSA.
Results: Groups did not differ for age, bone age or height. BMI-SDS was lower in AN boys than controls (-1.15±0.42 vs. 0.09±0.76 kg/m^2, p< 0.0001). As previously reported, a larger proportion of AN boys had BMD Z-scores < -1 at the femoral neck (60% vs. 12.5%, p=0008). Using HSA, at the narrow neck and trochanteric region, boys with AN had lower cross-sectional area (estimate of resistance to axial forces) (p=0.03, 0.02) and cortical thickness (p=0.02, 0.03), and a lower neck shaft angle (p=0.047). Buckling ratio at the trochanteric region was higher in AN (p=0.008). Subperiosteal and endocortical width, cross-sectional moment of inertia (estimates resistance to bending forces) and section modulus (index of strength of bending) did not differ. AN boys had lower testosterone (p=0.0005) and estradiol (p=0.006), but did not differ for IGF-1. Strongest associations of HSA measures were observed with lean mass, testosterone and estradiol. On multivariate analysis with lean mass, testosterone and estradiol entered into the model, lean mass remained positively associated with most HSA measures.
Conclusions: Boys with AN have impaired hip geometric parameters, driven by lower lean mass.

P1-d1-307 Fat Metabolism, Obesity 1

Use of a sex- and ethnicity-specific childhood continuous metabolic syndrome risk score to detect risk of glucose intolerance

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Background: The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors that increase risk for Type 2 diabetes and cardiovascular disease. While traditional criteria for MetS have been based on cut-off points for these factors, we have recently formulated an ethnicity- and gender-specific continuous childhood MetS (CC-MetS) risk score that avoids discrepancies seen for traditional criteria.
Objective and hypotheses: Our CC-MetS score will exhibit improved sensitivity to detect adolescents with glucose intolerance (gluc-int), a forerunner to diabetes.
Methods: Using 2005-2010 data from the National Health and Nutrition Examination Survey (NHANES), we assessed relationships between CC-MetS score and gluc-int (a glucose of ≥140 mg/dL at 2 hrs after a glucola load) among adolescents age 12-20. We assessed ROC-curves for prediction of gluc-int and compared sensitivity and specificity of the CC-MetS score vs. traditional MetS criteria for identifying individuals with gluc-int.
Results: Of 1,153 adolescents eligible for analysis, 72 (4.7%) had a gluc-int. Mean CC-MetS score values for those with vs. without gluc-int were 0.28 vs. -0.03. Our CC-MetS score had an area-under-the-ROC curve of 0.66 for the identification of adolescents with gluc-int. Using a cut-off 0.75, the CC-MetS score (of which 16.6% of the sample were above this point) had a 35.6% sensitivity and 84.3% specificity for identification of adolescents with gluc-int, compared to traditional ATP-III-based sensitivity and specificity of 23.7% and 92.9%.
Conclusions: Our ethnicity- and gender-specific CC-MetS score was more sensitive than ATP-III criteria at identifying adolescents with gluc-int. Following further validation this score could potentially be used to identify children at higher risk for developing adult diseases related to MetS, who could then be targeted for increased intervention. Additionally, the score provides a powerful new outcome for use in childhood obesity and MetS research.

P1-d1-308 Fat Metabolism, Obesity 1

Exposure to androgens during early development predisposes females to hypothalamic gliosis and metabolic syndrome

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Background: Hypothalamic inflammation and gliosis are hypothesized to participate in development of metabolic syndrome. Hypothalamic astrocytes are sexually dimorphic, with those from males being more prone to activation in response to metabolic challenges.
Objective and hypotheses: We hypothesized that excess androgens during development masculinize female astrocytes making them more susceptible to metabolic insults. We aimed to characterize the correlation between changes in weight/fat gain and astrocytic markers after neonatal testosterone exposure.
Methods: On postnatal day (PND) 1 female rats were injected with testosterone propionate [208mg/kg; androgenized females (AF)] or vehicle (F). Males (M) received vehicle. Half of each group was killed on PND10 and half on PND90. Body weight, length, fat pads, glycemia and circulating cytokines were measured and the hypothalamus removed and processed.
Results: At PND10 there were no differences in body weight, length, glycemia or circulating interleukin (IL)1β, IL6 or TNFα levels. Compared to M both F and AF had more subcutaneous adipose tissue (SCA), with AF the highest levels ($p< 0.0001$). Leptin levels were also higher in both F and AF ($p< 0.01$). The astrocyte markers glial fibrillary acidic protein (GFAP) and vimentin were unaffected in the hypothalamus. At PND90 M and AF weighed more than F ($p< 0.0001$). Males had more SCA and visceral fat and higher leptin levels (all $p< 0.0001$) than F and AF. Although AF did not have more fat than F, they had higher leptin and IL1β ($p< 0.005$) levels, with AF having IL1β levels indistinguishable from M. Hypothalamic GFAP ($p< 0.01$) and vimentin ($p< 0.001$) levels were higher in M than F and neonatal androgenization increased these parameters.
Conclusions: These central modifications may be involved in perpetuating the metabolic outcomes observed in androgenized females, as astrogliosis is suggested to participate in development of obesity and hypothalamic insulin/leptin insensitivity.

P1-d1-309 Fat Metabolism, Obesity 1

A new human adipocyte model derived from a PTEN-deficient lipoma

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Objective: Human adipocyte models are needed for investigating molecular mechanisms of adiposity development. We aimed to establish a new human adipocyte model termed LipPD1 derived from a PTEN-deficient lipoma. The results will be compared with the well established human SGBS preadipocyte strain in respect to functional and signaling analysis.
Methods: Gene expression was analysed using quantitative *real-time* PCR. Adipose differentiation was determined by lipid staining and cell counting. Lipolysis rates were measured by glycerol release after stimulation with isoproterenol. Insulin stimulated glucose uptake was quantified by measuring ^{14}C-labelled 2-deoxyglucose uptake. Phosphoinositide-3-kinase (PI3K) activity was determined by applying fluorescence redistribution after photobleaching (FRAP)/total internal reflection fluorescence (TIRF).
Results: LipPD1 preadipocytes had a lifespan of 91 population doublings with a doubling time of 25h. The expression of the adipocyte markers PPARγ, FASN, adiponectin and ap2 during differentiation was not significantly different but tended to be increased in LipPD1 compared to SGBS cells. Functional analysis revealed no significant differences between LipPD1 and SGBS cells in 2-deoxyglucose uptake after insulin stimulation and lipolysis after stimulation by isoproterenol. LipPD1 preadipocytes preserved a capacity for adipocyte differentiation of 55.1±4.2% for 29 PD. A fluorescent biomarker, reflecting PI3K activity by redistribution to the plasma membrane, was found membrane-associated to a higher amount in LipPD1 (33.4±2.7%) compared to SGBS adipocytes (20.9±2.3%). A constitutive activation of the kinase AKT was found by detecting increased Ser473 and Thr308 phosphorylation in LipPD1 cells.
Conclusions: LipPD1 cells have increased PI3K/AKT activity compared to SGBS. LipPD1 preadipocytes show a high potential for adipose differentiation and a prolonged lifespan and are a suitable model to investigate molecular mechanisms of obesity.

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Renin-angiotensin-aldosterone axis and cortisoluria in obese children and adolescents with or without arterial hypertension measured by 24-hour ambulatory blood pressure monitoring (ABPM)

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Background: Obesity is associated with significant comorbities such as arterial hypertension (AHT). Activation of the renin-angiotensin-aldosterone axis has been associated with physiological mechanisms of AHT; however, this remains to be elucidated in children. ABPM is a useful non-invasive method of evaluating blood pressure (BP).
Objective: To analyse the renin-angiotensin-aldosterone axis in a population of obese children and adolescents with and without AHT measured by ABPM and evaluate serum cortisol and 24- hour urine cortisol.
Methods: 129 children and adolescents (74 boys, 48 prepubertal, mean age 11.9 ± 2.5 with non-syndromic obesity were included. Anthropometric parameters were taken and serum electrolytes, TSH, free T4, renin and cortisol were determined. 24-hour aldosterone and cortisol in urine were determined in 63 and 59 patients, respectively. ABPM was used to diagnose AHT when more than 25% of measurements exceeded the threshold according to height, sex and age.
Results: 52 patients presented systolic and/or diastolic AHT. Serum aldosterone showed significant differences with mean levels of 26 ng/dL and 19.6 ng/dL in hypertensive and normotensive patients, respectively (p=0.02). Urine aldosterone levels were significantly higher in hypertensive obese patients (16.9 mg/24h) than in non-hypertensive obese patients (9.8 mg/24h) (p=0.003). Urinary cortisol was 79.8 mg/24h in hypertensive patients and 41.1 mg/24h (p=0.013) in normotensive patients.
Conclusions: Serum and urinary aldosterone and urinary cortisol were raised in obese children with AHT. These results provide new data on abnormal urinary aldosterone and cortisol, which might implicate the renin-angiotensin-aldosterone and hypothalamus-hypophyseal-adrenal axes in the aetiology of AHT in obese children and adolescents. Further studies are required to analyse relationships between obesity, hypertension and y anomalous steroid excretion in urine.

P1-d1-311 Fat Metabolism, Obesity 1

Up-regulation of hippocampal somatostatin receptors may attenuate acute leptin action after its central infusion

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Background: Leptin and somatostatin have opposite functions in the modulation of food ingestive behavior that is partially regulated in the hippocampus. Although it is known that acute leptin-mediated suppression of food intake decreases with time, the counter-regulatory mechanisms in this brain area remain unclear.
Objective and hypotheses: As the somatostatinergic system may counteract brain leptin signaling, our aim was to analyze the effect of acute central leptin infusion on the somatostatin receptor-effector system and its relationship with leptin related-intracellular signaling.
Methods: We studied 10 male Wister rats including controls (C) and those treated icv with a single dose of 5 µg of leptin (L) and sacrificed 6 h later. Hippocampal somatostatin receptors (sst) were measured by a binding assay, activity of adenylyl cyclase (AC) by a functional assay and sst1-4, α subunits 1-3 of inhibitory G proteins (Gi) and suppressor of cytokine signaling 3 (SOCS3) levels by Western blot. The levels of c-Jun and activation of signal transducer and activator of transcription 3 (STAT3), c-Jun N-terminal kinase (JNK) and cyclic AMP response element binding protein (CREB) were determined in the hippocampus by a multiplexed bead immunoassay.
Results: The somatostatin receptor density was increased in L group due to changes in sst2 levels. These variations were concomitant with increased activation of JNK and CREB and levels of c-Jun. The levels of sst2 correlated with an elevated capacity of somatostatin to inhibit forskolin-stimulated AC activity. Activation of STAT3 and levels of α subunits of Gi proteins and SOCS3 remained unchanged in the hippocampus.
Conclusions: Somatostatin may antagonize leptin's actions in the rat hippocampus.

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GPR120 R270H polymorphism is a risk factor for liver injury in obese children

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Background: Omega 3 Fatty Acid Receptor-1 (O3FAR1/GPR120) is a receptor for polyunsaturated fatty acid (PUFA). It's a G-protein coupled receptor involved in several metabolic processes. Furthermore a variant of the GPR120 (R270H) enhances inflammation in adipose tissue which leads to insulin-resistance in murine model.
Objective and hypotheses: To investigate the association between the R270H variant and glucose homeostasis, liver enzymes and metabolic syndrome components in obese children and adolescents.
Methods: 581 obese children were enrolled (age 10.15±6.6; BMI Z-Score 3.76±2). Waist Circumference, OGTT, blood pressure, HDL-cholesterol, triglycerides, liver enzymes, insulin and HOMA were measured. Steatosis was evaluated by US. DNA was extracted from nucleated white cells, a TaqMan assay was performed to reveal the polymorphism R270H.
Results: Despite studies on mice, obese children carrying the 270H allele didn't show association with IR ($p>0.05$), steatosis ($p>0.05$) and metabolic syndrome components ($p>0.05$) compared to obese children homozygotes for the wild allele. Furthermore our results demonstrate a statistical association to higher ALT levels. ALT≥40U/mL was present in 40% (8/20) of children with the 270H allele and in 17% (96/556) of children with wild type allele. χ^2 test was 6.7 ($p=0,009$). Odds Ratio for ALT≥40U/mL was 3.2 (IC=1.2-8.0).
Conclusions: Our study didn't prove any association with IR, IGT and steatosis, but we found an association with increased levels of ALT, suggesting a role of the GPR120 in the pathogenesis of liver inflammation. PUFA are involved in anti-inflammatory processes mediated by GPR120 as membrane receptor inhibiting the NFkB which suppresses gene replication. Therefore production of inflammation mediators is reduced. This is the first study which investigates linkages between R270H and several metabolic parameters in children and demonstrates that the polymorphism R270H of GPR120 is a risk factor for liver injury.

P1-d1-313 Fat Metabolism, Obesity 1

Role of oncostatin M, a novel gp130 cytokine secreted in adipose tissue, in the development of obesity and type 2 diabetes

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Background: Adipose tissue is a highly active endocrine organ secreting several factors that comprise a new hormonal network linking adipose tissue with other tissues. The adipocytes, the primary constituent of adipose tissue, are responsive to several gp130 cytokines, which have been targeted as potential therapeutic agents in obesity. Oncostatin m (OSM) is one of these cytokines, but its effects on adipocytes have not been previously examined.
Objective: To assess the effects of OSM *in vitro* (adipocytes) and to examine its expression *in vivo* (adipose tissue from mice and humans with obesity-induced insulin resistance).
Methods: *In vitro:* Murine 3T3-L1 pre-adipocytes were treated with OSM in different conditions and cell monolayers were harvested to test activation of STATs by western blot, and PAI-1 and IL-6 gene expression by PCR.
In vivo: Animals- Fifty male C57BL/6J mice 6 weeks of age were fed either low- or high-fat diets for 2, 4, 6 and 12 wk. Visceral adipose tissue was isolated to examine OSM levels by western blot. *Humans*- Subcutaneous and visceral adipose tissue from obese patients prior to bariatric surgery were used to assess OSM gene expression by PCR.
Results: OSM was up-regulated in adipose tissue of obese/type 2 diabetic mice and humans. The specific OSM receptor (OSMRb) was identified in adipocytes demonstrating that OSM activates STAT5 in a dose-dependent manner. In addition, OSM induced the expression of target genes implicated in metabolic diseases, such as PAI-1 and IL-6.
Conclusion: These novel findings suggest a key role of OSM in the development of metabolic disorders.

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Novel variants of aquaglyceroporin 7 (AQP7) gene promoter in relation to serum glycerol and susceptibility to low birth weight and type 2 diabetes in prepubertal children and adolescents

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Background: AQP7 regulated adipocyte glycerol efflux influences lipid and glucose homeostasis. Impaired AQP7 expression leads to adipocyte hypertrophy,whereas AQP7gene promoter variants may lead to impaired transcriptional regulation of AQP7. Metabolically "unhealthy" adipose tissue may indicate impaired HDL lipidation and biogenesis.
Objective and hypotheses: To identify possible AQP7 promoter SNPs in lean and obese children.

Methods: Genomic DNA was extracted from the blood of 37 obese and 61 lean children and adolescents.The samples were sequenced for promoter region -2580*(2421)* to -1161*(3840)* of AQP7. The mRNA and protein expression of AQP7 was studied by RT-PCR and western immunoblotting, respectively. Serum insulin and glycerol were measured by ELISA.
Results: One novel mutation was identified: -2185(*T2816A)*, in an obese prepubertal patient with extremely low AQP7mRNA expression, extremely high levels of serum glycerol and low insulin levels. Also several novel SNPs were identified: -2291*(A2710G)*, -2219*(C2782A)*, -2091*(C2910)*, -1932*(G3069A)* and one -1884*(C3117T)* with rs3758268. Individuals that were heterozygous for SNPs -2291*(A2710G)*, -2219*(C2782A)*, -2091*(C2910)* and -1884*(C3117T)* had lower HDL levels (p=0.001) and similar glycerol levels, compared to the individuals that were homozygous for the 4 wild type alleles, irrespective of BMI but related to a positive family history of type 2 diabetes (T2DFH) (18.8%vs 2.3%, p< 0.001) and low birth weight for gestational age [*(SGA)*16.7%vs 5.2%*(AGA)*, p=0.045].
Conclusions: The novel mutation -2185(*T2816A)* might be associated with the lower gene expression of AQP7 and high levels of serum glycerol, that possibly contribute to the obese phenotype. The novel heterozygotic combination of the four polymorphisms -2291*(A2710G)*, -2219*(C2782A)*, -2091*(C2910)* and -1884*(C3117T)* in SGA children and adolescents with low HDL and positive T2DFH might reflect a higher susceptibility for developing "unhealthy" adipose tissue and T2D.

P1-d1-315 Fat Metabolism, Obesity 1

Diet supplementation with betaine during lactation prevents the development of glucose intolerance in a mouse model of childhood obesity

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Background: Excessive energy intake and rapid weight gain early in life are associated with obesity and type2 diabetes. Betaine, a choline derivate found in some vegetables, is a methyl donor that might influence DNA methylation. Furthermore, betaine deficiency has been associated with obesity, and its administration to animal models improves insulin sensitivity.
Objective: To prevent the diabetic phenotype in a mouse model of childhood obesity by administering betaine to mothers exclusively during lactation.
Methods: We have previously described a mouse model of neonatal overfeeding and accelerated growth (ON) that develops obesity and glucose intolerance with aging. Here, we have supplemented the drinking water of dams with betaine during lactation to influence the metabolism of their offspring. At weaning all offspring received standard chow.
Results: Offspring of betaine-supplemented dams (ON+B) showed similar neonatal growth rate and adult body weight to ON mice (5-8 months). However, glucose tolerance and insulin levels were normalized in adult ON+B mice (Table 1). Adult ON mice developed adipocyte hypertrophy, increased secretion of pro-inflammatory adipokines and leptin and increased gene expression in the adipose tissue (Table1). Adipokine gene expression and secretion pattern were normalized in 8 month-old ON+B mice (Table 1).

	C	ON	ON+B
Insulin (ng/ml)	0.47± 0.07	0.95±0.42*	0.45±0.13*
TNFα (pg/mL)	13±10	25±7	2.2±1*
Leptin (ng/ml)	1.03±0.37	5.94±1.26*	0.92±0.08*
TNFα mRNA	1±0.26	1.56±0.21	0.74±0.20*
Leptin mRNA	1±0.26	1.88±0.30*	0.43±0.18*

[Table 1]

Conclusions: Administration of betaine to our mouse model, exclusively during lactation, has long-term beneficial effects preventing insulin resistance and glucose intolerance later in life. Therefore, interventions during early phases of development should be considered when designing strategies to prevent metabolic complications in adults.

P1-d1-316 Fat Metabolism, Obesity 1

Higher serum levels of the Wnt-signaling antagonist DKK1 in obese compared to Prader-Willi syndrome

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Background: Obesity and in particular visceral adiposity has been related to low bone mineral density (BMD) and greater fracture risk. Subjects with Prader Willi syndrome (PWS) have lower amount of visceral fat than patients with simple obesity, however can develop osteoporosis. A strong relationship between inhibition of the osteoblast formation and induction of the adipocyte differentiation has been demonstrated. Inhibitors of osteoblastogenesis, such as Dickkopf-1 (DKK1), a Wnt-signaling antagonist, can increase the formation of adipocytes.Objective and hypotheses. We aimed to analyze the serum levels as well as the expression of DKK1 in obese and in PWS subjects.
Methods: We studied by flow cytometry the expression of DKK1 in peripheral blood cells (PBCs) from 22 obese children (10 M, 9.5 ± 3.2 yrs, BMI SDS 1.9-2.6), 12 PWS adults (4 M, 29.5 ± 6.4 yrs, BMI 30.8-65.7 kg/m^2), 6 PWS children (2 M, 8.3 ± 3.0 yrs, BMI SDS 0.82-4.92), as well as 20 controls sex and age matched to obese and PWS children. DKK1 levels were also measured in the sera from patients and controls.
Results: Flow cytometry analysis demonstrated that monocytes, T lymphocytes and neutrophils from PWS and obese children expressed higher levels of DKK1 respect to controls (p< 0.01). Interestingly, serum DKK1 concentrations were significantly higher in obese children than in controls (p< 0.01), but not in PWS patients. Obese children showed an inverse correlation between BMD and abdominal obesity, and PWS adults showed a lower BMD than PWS children.
Conclusions: Our preliminary results highlight the high expression of DKK1 in PBCs from obese and PWS patients, which may have a prominent role in the increased fat depots in both of these subjects. Higher serum levels of DKK1 in obese than PWS subjects could explain the different distribution of adiposity in simply obesity respect to PWS.

P1-d1-317 Fat Metabolism, Obesity 1

Fitness and fatness have a biomarker in children: chemokine C-C ligand 2

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Background: Obesity is an epidemic impacting children globally. Obesity is associated with chronic low-grade inflammation with enhanced production of cytokines and chemokines. Chemokine C-C Ligand 2 (CCL2) is produced by immune and metabolic cells and attracts immune cells into metabolic organs, resulting in initiation and propagation of inflammation in obesity. How obesity and fitness affect the production of this chemokine in children is unknown.
Hypotheses: This study tested the hypotheses that CCL2 levels are higher in obese children when compared to lean controls, and that fitness modulates CCL2 levels allowing its use as a biomarker of fitness.
Methods: This was a cross sectional study conducted in a Pediatric Tertiary care center in Hamilton, Ontario, Canada. Overweight/obese children (BMI ≥ 85th percentile, n=18, 9 female, mean age 14.0±2.6 years) and lean controls (BMI< 85th percentile, n=18, 8 female, mean age 14.0±2.6 years) matched for age, sex and biological maturation were recruited from the obesity program and through community advertisements, respectively.
Aerobic fitness test was done using a cycle ergometer performing the McMaster All-Out Progressive Continuous Cycling test to exhaustion to determine peak oxygen uptake. Fasting CCL2 samples were taken prior to test and analyzed using ELISA.
Results: Obese participants had significantly higher CCL2 levels when compared to lean group (150.4±61.85 pg/ml versus 112.7±38 pg/ml, p-value 0.034).

To establish if CCL2 is a biomarker of fitness, we divided the groups based on their fitness levels. Obese high fitness group were similar to lean unfit and fit participants. Post-hoc analysis revealed that the overweight/obese low fitness group had significantly higher level of CCL2 compared to the lean low fitness group when adjusted to age, sex and maturity offset (F (3,29)=3.1, p=0.04).
Conclusions: CCL2 serves as a dual biomarker of inflammation and physical fitness in obese children.

P1-d1-318 Fat Metabolism, Obesity 1

Short-term intervention improves endothelial progenitor cell count and reduces cardiovascular markers in obese children and adolescents

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Background: Short term inpatient intervention is a treatment option for obesity during childhood and adolescents. Those interventions are cost intensive and studies at that age group are rare.
Objective and hypotheses: We aimed to analyze effects of a short term intervention on several cardiovascular parameters in obese children and adolescents.
Methods: We included 59 obese children and adolescents (BMI 29.57 +/- 4.36, BMI SDS 2.4 +/- 0.4) who participated in a short term intervention for 4-6 weeks, consisting of intensive dietary changes and physical activity. We measured anthropometrical data, analyzed the lipid profile, performed an OGTT and evaluated several cardiovascular parameters including 24h-RR, endothelial function as measured by reactive hyperemia (RHI), endothelial progenitor cells and cardiovascular markers before and after the intervention programme.
Results: After the intervention the patients' BMI was reduced by -1.71+/- 0.90, anthropometrical (waist, skin fold) and metabolic serum parameters (cholesterol, peak insulin) declined significantly. Systolic blood pressure (-5.88+/-10.27 mmHg) and heart rate (-5.15+/-7.53 bpm) were significantly lower. We identified a significant increase in protective endothelial progenitor cells (+37+/-116.06). Before the intervention 59.3% of the children showed signs for endothelial dysfunction, with a relatively low RHI. The RHI did not change significantly. The cardiovascular markers ICAM (-25.00+/-21.80) and E-Selectin (-11.25+/-10.72) and the inflammation marker hsCRP (-1.29+/- 2.00) decreased significantly.
Conclusions: Obese children and adolescents showed affected cardiovascular markers and endothelial dysfunction at that young age before intervention. Already a short-term intervention is very beneficial to improve several cardiovascular parameters. Obese children and adolescents should be included in such a programme if weight loss and its maintenance is not realizable at home.

P1-d2-319 Fat Metabolism, Obesity 2

Bariatric surgery in adolescents and young adults

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Background: To date, the only effective treatment to achieve sustained weight loss in adults with morbid obesity is bariatric surgery. While considered experimental, its use in adolescents is increasing worldwide.
Objective: Our aim was to determine the safety and effectiveness of adolescent bariatric surgery, and to improve treatment recommendations for this age group.
Methods: Since 2005, patients undergoing bariatric surgery in Germany are entered in a registry "study for quality assurance in obesity surgeries". We conducted a descriptive analysis including patients up to the age of 21 years from Jan 2005 to Dec 2010.
Results: 345 procedures were recorded by 58 different hospitals. N=51 patients were under the age of 18 yrs. The most common surgical techniques were gastric banding (n=118, 34.2%), gastric bypass (n=116, 33.6%), and sleeve gastrectomy (n=78, 22.6%). Short-term complications (intra-operative; general postoperative; specific postoperative) were slightly lower for gastric banding (0.8%; 2.5%; 0.8%) than for gastric bypass (2.6%; 5.2%; 1.7%) or sleeve gastrectomy (0%; 9.0%; 7.7%). Follow-up information was recorded for 48% (n=167) of patients. In accordance with published findings, weight- and BMI reduction were lower for gastric banding (-28kg; -9.5kg/m^2) compared to gastric bypass (-50kg; -16.4kg/m^2) or sleeve gastrectomy (-46kg; -15.4kg/m^2). Outcomes did not differ between the < 18 and ≥ 18 year old patients.
Conclusion: Like in adults, bariatric surgery results in significant weight loss in adolescents. However, the low follow up rates and missing long-term observations prohibit a final conclusion about the long-term effectiveness and safety. Clinical trials with structured surgical programs and mechanisms to ascertain patient adherence are needed to derive at a final conclusion.
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P1-d2-320 Fat Metabolism, Obesity 2

Leptin substitution results in increased insulin and changes in gut hormone secretion, but unchanged BDNF in an adolescent with leptin deficiency

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Background: Leptin deficiency (LD) leads to profoundly disturbed energy homeostasis and hyperphagia which can be successfully treated by leptin substitution alone. Brain-derived neurotrophic factor (BDNF) is a regulator of energy homeostasis and food intake downstream of hypothalamic leptin signaling. We tested the hypothesis that leptin treatment leads to increased secretion of BDNF and satiety gut hormones as well as decreased hunger hormone (ghrelin).
Methods: We evaluated the effect of recombinant leptin (metreleptin, Bristol-Myers-Squibb, New York City USA) substitution in a leptin-deficient morbidly obese 14.7 year old girl (leptin level below detection, homozygous mutation in the *LEP* gene) on changes of serum BDNF, insulin, glucagon-like peptide-1 (GLP-1), ghrelin, and peptide-YY (PYY), before as well as 11 and 46 weeks after start of metreleptin treatment . Hormone secretion was evaluated in 30 min intervals for 10 h (0730-1730) to calculate the area under the curve before and after breakfast/lunch.
Results:

Measures in relation to start of leptin therapy	Start	+ 11 weeks (% change from start)	+ 46 weeks (% change from start)
Weight (kg)	103.4	-12.5 %	-20.7 %
BMI (kg/m2)	35.4	-12.1 %	-24 %
Ad libitum test meal (kcal)	1899	-14.2 %	-21.1 %
Body fat mass (%)(DEXA)	50.1	-10.4 %	-21.6 %
BDNF AUC ng/mL x 10h	82.5	-2.7 %	-2.0 %
Insulin AUC ng/mL x 10h	28.7	+58.9 %	-44.8 %
GLP-1 AUC pg/mL x 10h	1542	+15.2 %	-33.7 %
Ghrelin AUC pg/mL x 10h	200	+5.5 %	-11 %
PYY AUC pg/mL x 10h	2010	+5 %	+13.2 %

[Metreleptin]

Conclusion: Leptin substitution resulted in strong weight and body fat reduction as well as increased satiety. The strong increase in insulin and GLP-1 secretion after 11 weeks of metreleptin treatment cannot be explained by reduced adiposity and might contribute to improved central satiety. Leptin

substitution does not seem to affect BDNF serum levels. Observed changes of PYY can lead to increased satiety but may be secondary to changes in weight status.

P1-d2-321 Fat Metabolism, Obesity 2

Neutrophil-to-lymphocyte ratio: ontogeny of a cardiovascular-risk marker

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Background: Low-grade chronic inflammation plays a pathogenic role in cardiovascular disease. An increase in the ratio of circulating neutrophils to lymphocytes (N/L) may cause endothelial dysfunction and serve as a marker of cardiovascular risk in adults.
Objective and hypotheses: We studied whether N/L associates with vascular features in children.
Methods: Subjects were 619 asymptomatic pre- or early-pubertal (Tanner 2 or 3) Caucasian children (326 boys and 293 girls) who were consecutively recruited in a setting of primary care. The subjects were stratified into three groups according to age [mean, 8.1 (range: 5-12 years)]. The N/L ratio was derived from the absolute neutrophil and lymphocyte counts. Body mass index (BMI), waist circumference, systolic blood pressure (SBP) and carotid intima-media thickness (cIMT) were assessed in all children.
Results: In children aged < 7 yr (n=206, all prepubertal), no associations were observed between N/L and either anthropometric or cardiovascular parameters. In children aged 7-9 yr (n=206, 5% early pubertal), higher N/L associated with higher BMI and waist circumference (both $p< 0.005$). In children aged >9 yr (n=207, 55% early pubertal), N/L ratio associated again with BMI and waist circumference and also positively with SBP and cIMT (all $p< 0.0001$). These associations remained significant after adjusting for confounding variables such as age, gender, BMI, waist, C-reactive protein and fasting triglycerides in linear regression models: SBP ($\beta=0.273$, $p< 0.001$; $r2=0.106$) and cIMT ($\beta=0.303$, $p< 0.001$; $r2=0.140$).
Conclusions: Our results provide the first evidence that increasing N/L ratio is associated with a less favorable cardiovascular profile from late childhood onwards.

P1-d2-322 Fat Metabolism, Obesity 2

Cardiovascular risk factors and carotid intima media thickness in prepubertal children

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Background: Even in children, early exposure to cardiovascular risk factors generates a chronic inflammatory state that could cause endothelial dysfunction and increase the carotid intima media thickness (CIMT).
Objectives: To investigate the CIMT and its relation to cardiovascular risk factors in prepubertal children with normal and excess weight.
Methods: Cross-sectional study with 80 obese, 18 overweight and 31 normal weight children. The mean, the median and the proportion of cardiovascular risk factors as well as CIMT were compared between obese, overweight and normal weight children and between children with insulin resistance and without.
Results: When comparing obese, overweight and normal weight children there was a difference in abdominal circumference ($p< 0,001$), systolic ($p< 0,001$) and diastolic blood pressure (BP) ($p=0,001$), HOMA-IR ($p=0,0001$), total cholesterol ($p=0,02$), HDL ($p=0,01$), LDL ($p=0,03$), triglycerides ($p=0,01$), C-reactive protein ($p< 0,001$), interleukin 6 ($p=0,02$), leptin ($p< 0,001$), and left CIMT ($p=0,03$).
When comparing children with insulin resistance with the ones without, there was a statistically significant difference between BMI Z-score ($p< 0,001$), abdominal circumference ($p< 0,001$), systolic ($p< 0,001$) and diastolic BP ($p< 0,006$), total cholesterol ($p< 0,001$), triglycerides ($p< 0,002$), and leptin ($p=0,004$).
The bivariate logistic regression showed a positive association ($p< 0.05$) between BMI Z-score, abdominal circumference, and systolic BP and the right, left and mean CIMT. The multivariate logistic regression demonstrated that the BMI Z-score ($p=0.02$) and the systolic BP ($p=0.04$) were positively associated with left CIMT. Systolic BP was also associated ($p=0.01$) with the mean CIMT.
Conclusion: These results demonstrate that cardiovascular risk factors are already present in prepubertal children with excess weight and affect the carotid intima media thickness.

P1-d2-323 Fat Metabolism, Obesity 2

Association between two genetic variants in APOA1 and CET and loss of adiposity after intervention in obese/overweight adolescents: Evasyon study

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Background: In recent years, several studies have shown the influence of some genetic variants and life style factors on the response to weight loss.
Objective and hypotheses: In this study, we examined the effect of two polymorphisms located in two genes involved in lipid metabolism (genes APOA1 y CETP), on fat loss after an interventional program for weight loss.
Methods: One hundred ninety-nine obese and overweight adolescents (age: 13-16 years, 39% male) followed a 12-week intervention program focus on weight loss: EVASYON study(www.estudioevasyon.com). This was a multidisciplinar intervention based on a caloric restriction diet (10-40%), increased physical activity and nutritional education. All subjects were studied for two SNPs in APOA1 (rs670) and CETP (rs1800777) genes using kitt N+S Nature System (Cinfa Laboratory).
Results: Using a regression model adjusted by age and sex, both polymorphisms (rs680 of APOA1 gene and rs1800777 of CETP gene) were significantly associated with decrease in BMI-SDS ($p=2.8 \times 10^{-10}$), waist circumference ($p=0.011$), fat mass loss ($p=2.9 \times 10^{-4}$) and waist/height index ($p=0.006$). Specifically, this model explained 25.2% of the BMI-SDS decrease after the intervention. Individually, both rs670 of ApoA1 gene ($B=-0.210$; $p=3.5 \times 10^{-5}$), and rs1800777 of CETP gene ($B=-0.507$; $p=0.003$) were significantly asociated with BMI-SDS decrease.
Conclusions: The response to an intervention for treating obesity and overweight in adolescents appears to be influenced by the presence of two SNPs in ApoA1 (rs670) and CETP (rs1800777) genes. This suggest that changes in lipid metabolism due to these genetic variants may be responsible for a better response to a multidisclipinar intervention to treat obesity and overweight.

P1-d2-324 Fat Metabolism, Obesity 2

Adipocyte oxidative stress produces glutathionylated lipid aldehydes, novel activators of macrophage inflammation

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Background: Obesity-associated insulin resistance has been linked to both adipocyte oxidative stress and adipose tissue inflammation. Oxidative stress leads to increased lipid peroxidation products. Among these, 4-hydroxy-2,3-trans-nonenal (HNE) is glutathionylated to produce glutathionylated-HNE (GSHNE) and its metabolite glutathionyl-1,4-dihydroxynonene (GSDHN).
Objective and hypotheses: GSHNE and GSDHN are:
1) produced under conditions of adipocyte oxidative stress,
2) are novel mediators of inflammation in macrophages.
Methods: Llipid peroxidation products were measured in 3T3-L1 adipocyte, RAW264.7 and peritoneal macrophages, and mouse adipose tissue by liquid chromatography-tandem mass spectrometry. Macrophage inflammation was assessed by measurement of TNFα ELISA and targeted microarray analysis of inflammatory genes. Insulin resistance measured by glucose tolerance test in high-fat fed mice.
Results:
1) GSHNE and GSDHN were produced by 3T3-L1 adipocytes in response to either high glucose or hydrogen peroxide.
2) Both GS-HNE and GS-DHN induced macrophage inflammation as measured by secretion of TNFα and leukotriene C_4.
3) GSHNE and GSDHN induced expression of several inflammatory genes in macrophages.
4) Higher levels of GSHNE were measured in visceral adipose tissue of high fat fed and ob/ob mice compared to lean controls.
5) Transgenic mice that overexpress glutathione-S-transferase A4 produce more GS-HNE than wild type mice. These mice have higher fasting glucose levels and moderately impaired glucose tolerance.
Conclusions: Oxidative stress in adipocytes results in the production of GSHNE and GSDHN. These glutathionylated lipid peroxidation products may represent a novel mechanism by which adipocyte dysfunction contributes to tissue inflammation and insulin resistance.

P1-d2-325 Fat Metabolism, Obesity 2

Increased metalloproteinase-9 activities (MMP-9) in children with metabolic syndrome (MS)

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Background: The development of inflammatory, pro-coagulants and IR surrogate markers has been associated with MS in adults, but has been little studied in children. No data exist in Metabolic Syndrome (MS) and remodeling of the extracellular matrix in children.
Metalloproteinase-9 activities (MMP-9) have been proposed as a biomarker of vulnerable plaques. Understanding the mechanisms of MS impact on MMPs is an interesting area of research to understanding of the complexity of MS.
Objective: To elucidate the behavior of plasma MMP-9 serum activities in children and its association with MS modified Cook's score.
Subjects and methods: A cross-sectional study including 278 children with aged between 5 and 16 years was designed. MS was defined by the modified Cook's criteria. MMP-9 serum activity was evaluated by zymography, and their association with MS modified Cook's score was analyzed with Spearman (*Rho*). The results are expressed as median [Q1-Q3].
Results: The prevalence of MS abnormalities was: score = 0 in 132 (47.5%), =1 in 76 (27.3%), =2 in 43 (15.5%), ≥3 in 27 (97%) subjects. A positive association was observed between MS score and MMP-9 (Rho = 0.221; $P< 0.001$). MMP-9 serum activity increase in children with higher MS score: Score 0= 1.58 [1.16 - 2.78]; 1= 1.56 [1.61-3.14]; 2= 2.40 [1.92-3.14] ; ≥3= 2.34 [1.39 - 2.83] (Kruskal-Wallis test; $P< 0.0001$). Dunn's multiple comparisons test, shown that subject with two or more MS abnormalities have higher MMP-9 serum activity ($P< 0.01$).
Conclusion: As far as we know, this is the first report in children showing a positive association between MS score and MMP-9. MMP-9 serum activity is increased in children with two or more MS abnormalities. This data suggest that remodeling of the extracellular matrix and vulnerable plaques biomarkers are early present in children with some components of MS.

P1-d2-326 Fat Metabolism, Obesity 2

Severe early-onset obesity caused by compound heterozygosity for two novel leptin receptor mutations

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Background: Recessive mutations of the leptin receptor (LEPR) are a rare cause of hyperphagia and severe early-onset obesity. Additional features are altered immune function, hypogonadotropic hypogonadism and low plasma IGF-I. Only 14 different mutations/deletions have been identified, and the phenotype has been described in 11 children.
Objectives: To study clinical and laboratory features of a child, compound heterozygous for two novel LEPR mutations (splicing mutation c.1753-1dup and missense mutation p.Ser723Phe) to further delineate the phenotype of LEPR deficiency in childhood.
Results: The girl was born with normal birth weight. Psychomotor development was normal. From baby onwards her appetite seemed insatiable and she gained weight quickly. At age 1.25 yr she weighed 19.6 kg (+6.4 SDS weight-for-height). Indirect calorimetry showed a resting energy expenditure of 570 kcal/day. A diet and exercise had some effect: weight at age 6.8 yr was 58.8 kg (+3.8 SDS weight-for-height), with a fat percentage of 44.6% measured by dexascan. Height and head circumference were +2.3 SDS (target height +0.8 SDS). Leptin was elevated to the level expected for this degree of obesity (43.9 ug/l at age 6.8 yr). She did not have frequent infections and lymphocyte subsets and T-cell proliferative responses were normal. Plasma IGF-I was normal. Her mother and sister, who carry the missense mutation, have normal weight but her father, who carries the splicing mutation, is obese (BMI 37.5 kg/m2) as has previously been reported in some heterozygous carriers. Both parents had a normal head circumference.
Conclusion: Compound heterozygosity for two novel LEPR mutations results in hyperphagia and obesity in this girl. However, she has no immune defect in contrast to 9 of 11 previously studied LEPR deficient children. Head circumference was not reported in other patients, so it is unclear whether macrocephaly is related to LEPR deficiency.

P1-d2-327 Fat Metabolism, Obesity 2

Is increased insulin sensitivity in Prader-Willi syndrome due to hyperghrelinemia?

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Background: Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder arising from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13. Obesity represents one of the most serious symptoms of the PWS, leading to develop premature mortality from its complications.
Objective and hypotheses: To compare parameters of lipid, carbohydrate metabolism and ghrelin levels in 15 children non-GH-treated patients with genetically confirmed PWS with 15 age, sex and BMI-matched non-PWS obese controls (OC).

Methods: All patients (PWS and OC) underwent anthropometric examination and measurement of serum glucose and insulin levels during standard oral glucose tolerance test, fasting and postprandial ghrelin during mixed meal-test, lipids and leptin and associations between variables.
Results: PWS(5M:10F) vs OC (4M:11F) were similar in age (11[7,8-13,9] vs (11,6[9,5-13,8]yrs), BMI (3,26 vs 3,2 SDS) and leptin levels (85,2 vs 75,4 ng/ml).
By contrast, IGF-1 levels were lower in PWS patients (94[74,6÷208,2]) vs (236[177÷387]); Fasting glucose concentrations (4,6 [4,3÷4,9]) vs (4,9 [4,7÷5,1]) and HOMA-IR(1,4 [0,9÷2,6]) vs (2,85 [2,47÷4,15]) were lower; and Matsuda-IR 4,8 [3,03÷8,1] was higher in PWS compared with OC (2,97 [2,19÷3,96]), suggesting that PWS children are more insulin sensitive than OC. Insulin levels on OGTT were lower in PWS than in non-PWS obese group, but the difference was not significant in this cohort of patients. Hyperghrelinemia (fasting and postprandial) was observed in our patients with PWS.Fasting ghrelin was significantly negatively correlated with fasting glucose in the PWS and OC groups (-0,59 and -0,92) and in PWS with IGF-1 level (-0,79).
Conclusions: Glucoregulatory mechanisms are different in obese PWS versus non-PWS subjects. Further long-term studies are needed to determine whether or not the apparent insulin sensitivity in PWS subjects may be due to their hyperghrelinemia.

P1-d2-328 Fat Metabolism, Obesity 2

Endocrine counter-regulation after weight-loss in obese children and adolescents: a controlled trial

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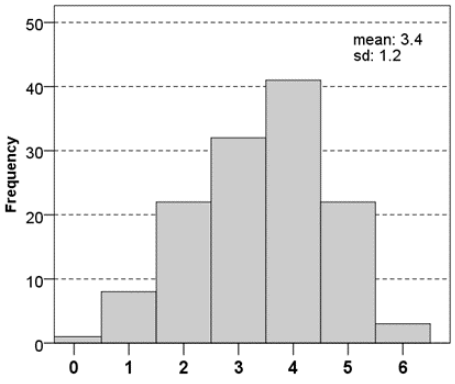
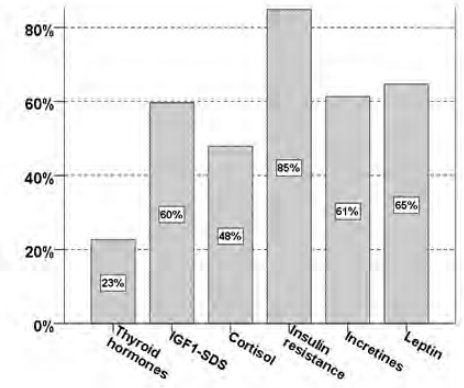
Background: Lifestyle interventions show a sustained body weight reduction in only 10-20% of obese children and adolescents.
Objective and hypotheses: As shown in adult obese patients an endogenous, endocrine response to weight loss is a major obstacle for long-term weight maintenance (e.g. reduction of leptin and thyroid hormones). To assess the hormonal counter-regulation during weight loss in the pediatric obese population we conducted a controlled pediatric weight intervention trial.
Methods: We included 153 obese children/adolescents (14±1.9 yrs; 53% female; BMI 31±4.0 kg/m²) into a multiprofessional lifestyle intervention program. 143 children finally met the criteria as defined by at least -0.2 BMI-SDS during the 3-months weight loss period. Hormonal counter-regulation was defined for six hormonal circuits modified by body weight reduction (*thyroid axis*: Δ TSH< 0 & Δ fT4≤0; *IGF1 axis*: Δ IGF1-SDS>0; *adrenal gland axis*: Δ cortisol>0; *insulin resistance*: ΔHOMA< 0; *incretines*: ΔGIP< 0; *leptin*: the two highest tertiles of Δ leptin).
Results: In 98% counter-regulation affected at least 2 hormonal circuits. Change of insulin resistance as well as leptin levels was frequent, with significant correlation between decrease of leptin and BMI-SDS-reduction (r=0.42;



[Figure: A: Frequency of subjects zero to six counter-regulating hormonal axes.]



[Figure: B: Prevalence of responding children and adolescents regarding to different counter-regulating hormonal axes.]

Conclusions: In almost all pediatric participants an endocrine counter-regulation occurred after weight loss, underlying the dynamic of hormonal adaptation processes already in childhood obesity. The ongoing study will clarify if the individual hormonal counter-regulation predict weight maintenance or regain in a long-term perspective.

P1-d2-329 Fat Metabolism, Obesity 2

The smallest paternally transmitted SNORD 116 deletion in a young female displays a typical Prader-Willi syndrome phenotype

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Introduction: Prader-Willi syndrome (PWS) is a rare disorder arising from the lack of expression of paternal alleles in the chromosomal region 15q11-13. Three clinical cases with microdeletion have been recently reported.
Case study: We report the case of a 23-years old woman, of Caucasian origin. The patient was born after 36 weeks of gestation, by a scheduled C-section because of the presence of last trimester polyhydramnios. Birth weight was 2780 g, length 48 cm and head circumference 35 cm. Severe neonatal hypotonia was noted after birth with poor suckling requiring complete nasogastric tube feeding for the first 2 weeks of life. A first baby born from the couple was a preterm girl who died for unknown reasons on the fourth day of life and presented a severe hypotonia.
The patient was admitted in our reference centre for PWS when she was 23. Height was 155 cm
(-1.5 SD,), weight 75 kg, BMI 31.2 kg/m² and head circumference 59 cm (+2.5 SD). She was blond haired with narrow front and had mild dysmorphic features. She has no autonomy to control her hyperphagia and displays temper tantrums with difficulties for planification. Her endocrine evaluation confirmed a growth hormone deficiency, hypogonadism and hypothyroidism. The diagnostic testing for PWS with a methyl specific PCR based at the SNURF-SNRPN locus was normal. Because we considered she presented a PWS consistent phenotype we decided to complete the genetic study by performing a home made 15q11q12 QMPSF assay (Quantitative Multiplex PCR of Short fluorescent Fragment) This technics showed a 118 kbp microdeletion in the SNORD116 locus . To our knowledge it is the shortest microdeletion of SNORD116 locus and the first transmitted by the asymptomatic father and the first female report.
Conclusion: We confirmed that the small region for PWS including the SNORD 116 gene drives the PWS phenotype in human and that deletion of the snord116 gene locus should be searched in all patients with PW-like syndrome.

P1-d2-330 Fat Metabolism, Obesity 2

Abstract has been withdrawn

P1-d3-331 Fat Metabolism, Obesity 3

Deep breathing acutely improves arterial dysfunction in obese children: evidence of functional impairment

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Background and aim: Similarly to type 2 diabetes, patients with obesity show insulin resistance, autonomic and vascular abnormalities associated with increased morbidity and mortality.
The aim of this study was to test whether arterial dysfunction in obese children may have a functional nature, reversible with appropriate interventions, and to investigate whether metabolic status were associated with the abnormalities. For this purpose, we tested whether deep-breathing (an intervention known to reduce sympathetic activity) could acutely improve arterial function.
Materials and methods: 130 Caucasian obese children (67 females, 63 males; mean age 11.5±2.9 yr, BMI > 95th percentile) and 67 age-matched healthy normal-weight control children (31 females, 36 males), were recruited. We measured markers of metabolic syndrome, augmentation index (AIx), blood pressure contour and pulse wave velocity during spontaneous and controlled breathing.
Results: Individual measure of average AIx showed increased values in obese male participants as compared with the control group. Slow breathing acutely reduced AIx, to a greater extent than in normal-weight control. Similarly, blood pressure contour showed higher values in obese children that were significantly attenuated by slow breathing. Baseline pulse wave velocity was not altered in obese participants. Markers of metabolic syndrome were correlated to AIx and pulse wave velocity.
Conclusions: Obese subjects (mainly male) showed impaired of in arterial function parameters, however this alteration was largely functional, likely related to autonomic dysfunction and to metabolic abnormalities. The acute improvement in vascular abnormalities with reduction in sympathetic activity suggests potential strategies to prevent sympathetic modulation and the development of clinical disease.

P1-d3-332 Fat Metabolism, Obesity 3

Consumption of sugar-sweetened beverages is associated with prospective weight gain in preschoolers

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Background: While sugar-sweetened beverage (SSB) consumption has been tightly linked to weight status among older children, the data regarding these relationships in preschoolers and kindergarteners has been mixed.
Objective and hypotheses: Our objective was to evaluate longitudinal and cross-sectional relationships between SSB consumption and weight status among children age 2-5 years, with a hypothesis that consumption of SSB would be associated with higher BMI z-scores cross-sectionally and a greater increase in BMI z-score over time in longitudinal analysis.
Methods: We assessed SSB consumption and BMI z-scores among 8300 children followed prospectively in the Early Childhood Longitudinal Survey-Birth Cohort. We used linear and logistic regression and adjusted for race/ethnicity, socioeconomic status, mother's BMI and television viewing.
Results: As compared to non-drinkers, children drinking 2 servings of SSB daily had higher BMI z-scores among children age 4 (0.62 vs. 0.80, $p< 0.05$) and 5 (0.60 vs. 0.85, $p< 0.001$). Children age 5 who drank SSB (compared to non-drinkers) had a higher odds ratio for being obese (OR 1.43, confidence interval 1.10-1.85, $p< 0.01$). In prospective analysis, children drinking SSB at 2 years (compared to non-drinkers) had a greater subsequent increase in BMI z-score over the ensuing 2 years (+0.18 vs. +0.32, $p< 0.05$).
Conclusions: Similar to what is seen among older children, preschoolers and kindergarteners drinking SSB demonstrate both prospective and cross-sectional correlations with higher BMI z-score. Pediatricians and parents should discourage SSB consumption to avoid potential unhealthy weight gain in young children.

P1-d3-333 Fat Metabolism, Obesity 3

Central leptin infusion increases insulin sensitivity and glycogen levels in the rat liver

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Background: Leptin modifies hepatic carbohydrate metabolism and its icv infusion reduces the increase in glycaemia induced by central insulin infusion. However, the central effects of leptin on insulin sensitivity and the relationship with carbohydrate metabolism in the liver remain unknown.
Objective and hypotheses: We hypothesized that leptin modulates hepatic insulin sensitivity. Thus, we studied the effect of central leptin infusion on insulin signaling and the relation with glucose uptake and glycogen levels in the liver.
Methods: Thirty-six male Wistar rats were divided into control (C), icv leptin infusion (12 µg/day) for 14 days (L) and pair-fed (PF) groups. These groups were treated with vehicle or a single icv dose of 10 mU of rapid insulin (I, PFI and L+I, respectively). The animals were sacrificed 2 hours later. We studied the hepatic levels of glucose transporter 2 (GLUT2), phosphoenolpyruvate carboxykinase (PEPCK) and glycogen synthase kinase (GSK) by Western blot and the phosphorylated and total levels of signal transducer and activator of transcription 3 (STAT3), cyclic AMP response element binding protein (CREB), insulin receptor substrate 1 (IRS1) and Akt by multiplexed bead immunoassay. Hepatic glycogen levels were measured by a colorimetric method after acid hydrolysis.
Results: Levels of GLUT2 were increased ($p< 0.05$) and PEPCK decreased in L, I and L + I rats ($p< 0.05$). GSK levels were reduced in L and L+I ($p < 0.01$), while STAT3 activation was decreased in all groups ($p< 0.01$). Activation of CREB, IRS-1 and Akt was increased in l and L+I groups ($p< 0.001$, $p< 0.05$ and $p< 0.05$; respectively). Glycogen levels were decreased in PF and PFI and increased in L+I compared to C and L ($p< 0.01$).
Conclusions: Chronic central administration of leptin promotes hepatic carbohydrate anabolism through improved insulin sensitivity.

P1-d3-334 Fat Metabolism, Obesity 3

Clinical and genetic characteristics of the paediatric heterozygous familial hypercholesterolaemia population in Slovenia: a preliminary report

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Background: Familial hypercholesterolemia (FH) is common inherited disorder (1/500) mainly caused by mutations in the low-density lipoprotein receptor (LDLR) gene. The residual *LDLR* activity varies considerably between mutations. Besides, around 10% of FH cases are caused by the mutations in

the *APOB* and *PCSK9* genes adding to the genotypic and the phenotypic variability. However, most of the children with FH are clinically asymptomatic. In children over eight years of age, the statins (HMG-CoA reductase inhibitors) are used as the first line treatment, effectively reducing the LDL-C values. In Slovenia, all the children at the age of five are screened for hypercholesterolemia, which is currently the only such nation-wide screening program.
Objectives: To present characteristics of the Slovene children and adolescents with FH and to assess the genotype-phenotype correlations.
Methods: All currently genetically confirmed pediatric patients from the Slovene national FH registry were included. The data on their phenotypic characteristics and on therapy was assessed. Lipid profiles were compared with regard to the type of mutation found.
Results: Fifty-seven patients were included in the study. Over 90% were referred through a national screening program at the age five. Forty-four patients had a spectrum of 24 causative *LDLR* mutations. Thirteen patients had mutation in *APOB* gene. Null *LDLR* mutations were associated with more elevated LDL cholesterol levels as compared to other *LDLR* mutations or *APOB* mutations. In patients over the age of eight, 29% had been prescribed diet only, 13% cholestyramine, 59% statins, 8% ezetimibe in addition to statins.
Conclusions: Over 90% of the FH patients were found through a national hypercholesterolemia screening program, proving it to be an effective strategy. Children with null *LDLR* alleles had more elevated LDL cholesterol levels than the others. Most of the FH patients over the age of eight were on statins.

P1-d3-335 Fat Metabolism, Obesity 3

Perinephric adipose tissue thickness in relation to blood pressure, plasma apelin and C-reactive protein levels in obese adolescents

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Background: Visceral adiposity plays an important role in the pathogenesis of obesity related hypertension. To our knowledge, measurement of perinephric adipose tissue (PNAT) thickness has not been studied so far.
Objectives: To define role of PNAT in hypertension; and to investigate its correlations with apelin, a newly identified adipokine, and C-reactive protein (CRP), a marker of inflammation.
Subjects and methods: Sixty obese adolescents and 29 healthy lean controls aging between 11 and 18 years were recruited. Study population was divided as hypertensive obese (Group 1) and normotensive obese subjects (Group 2) using 24-hour ambulatory blood pressure monitoring. PNAT was measured using ultrasonography bilaterally.
Results: PNAT thickness was found increased by 0.64 mm for each point of increase in body mass index (BMI). Plasma fasting apelin levels were significantly higher in Groups 1 and 2 than those in control group ($p < 0.001$ and $p = 0.004$, respectively). Mean BMI, plasma insulin and morning cortisol levels in Group 1 were significantly higher than in Group 2. Apelin was positively correlated with BMI and PNAT ($p = 0.003$ for both), and negatively correlated with pubertal stage ($r = -0.450$, $p < 0.001$) and age ($r = -0.258$ $p = 0.047$). CRP levels did not differ between study groups and controls and no correlation between apelin and CRP was found.
Conclusions: This is the first study showing direct relationship between PNAT, BMI and apelin in obese adolescents. Hypertension in this age group is closely related to degree of obesity. While plasma apelin increases in obesity, it decreases with increasing age and pubertal stage.

P1-d3-336 Fat Metabolism, Obesity 3

Direct TBI effects contribute to increased cardiovascular (CV) risk in adult survivors of childhood acute lymphoblastic leukaemia (ALL) treated with bone marrow transplantation and total body irradiation (BMT/TBI)

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Background: BMT/TBI survivors have poor CV health(SMR:10.4).
Objective: To investigate factors other than central obesity contributing to CV morbidity.
Method: ALL survivors, Group1 treated with BMT/TBI (10-14.4Gy) aged 9.3(1.0-10.8)y(n=21,11M), Group2 chemotherapy only (n=31,13M) were compared with Group3 simple obesity (n=30,10M). All were16-26y.
Investigations/outcomes:
1) Lipids [Triglyceride(TG), High Density Lipoprotein (HDL)]
2) Oral glucose tolerance test [Insulin resistance (IR)]
3) Arginine intravenous glucose tolerance tests [β-cell function (BCF)]
4) Abdominal MRI [Subcutaneous (sc), Visceral (Vis), Intramuscular (IM) fat%]
5) Pancreatic MRI [Pancreatic volume (PV)].
Analysis: ANOVA (post hoc Scheffé's tests), multiple regression, Pearson's correlations, at 5% significance.
Results: Group1 had higher prevalence of abnormal: glucose tolerance (43vs-0vs3%, p=0.001&0.006) & TG (48vs10vs13%, p=0.005&0.01) compared with groups 2&3; HDL (55vs27%, p=0.003) & IR (80vs10%, p=0.001) vs group2. Group1 had higher Vis, lower sc fat% vs Group3; and lower IM fat% vs Groups 2&3 (Table). Group1 vs 2&3 had more IR/Vis fat%, with lower pancreatic reserve (BCF/IR) correlating with smaller PV (r=0.3, p=0.01). HDL correlated negatively with sc (r=-0.36, p=0.002), Vis (r=-0.25, p=0.003) & IM (r=-0.23, p=0.048) fat%. TG correlated with Vis (r=0.35, p=0.002) & IM (r=0.32, p=0.006) fat%. More IM fat deposition is associated with less sc fat% [IM/total fat vs sc fat% (r=-0.53, p< 0.001)].

Variables: Mean(SD)* or Geometric mean (confidence interval)**	Group 1 (n=21)	Group 2 (n=31)	Group 3 (n=30)	1 vs 2 (p)	1 vs 3 (p)
Subcutaneous fat % *	37.9 (12.7)	45.5 (13.0)	59.5 (4.9)	0.07	<0.001
Visceral fat % *	15.5 (6.2)	12.1 (4.9)	11.7 (2.6)	0.06	0.04
Intramuscular fat % *	4.8 (1.6)	2.9 (0.8)	3.1 (1.0)	<0.001	<0.001
Pancreatic volume corrected for size (cm3/m2) *	19.9 (5.5)	24.9 (8.0)	25.6 (6.6)	0.048	0.03
Insulin resistance corrected for central adiposity (by ISIcomp per visceral fat)** (NB:↓ISIcomp=↑IR)	1.4 (1.1-1.8)	4.5 (3.7-5.6)	2.8 (2.2-3.6)	0.001	0.001
Beta cell response for level of IR (by AIR per ISIcomp**) (NB:↑AIR=↑BCF)	60.0 (43.8-76.7)	105.4 (79.8-138.4)	83.8 (69.7-100.9)	0.003	0.03

[Differential fat%, pancreatic volume & IR]

Conclusions: Greater IR/vis fat, reduced sc fat(reduced fat storage potential) and β-cell reserve(smaller pancreas) indicate direct effects of TBI(on muscle, fat, pancreas respectively) contribute to poor CV risk.

P1-d3-337 Fat Metabolism, Obesity 3

The role of gut microbiota in obesity aetiology. Cause or effect?

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Background: Recent studies have found differences in the composition and activity of gut microbiota between obese and lean individuals. However it is unclear whether these differences reflect a role of gut microbiota in obesity onset or these are an epiphenomenon of the different dietary patterns between obese and lean people.
Objective: This study addressed reverse causality in the results of previous studies by comparing the gut microbiota composition and concentration of bacterial metabolites in children with obesity of different aetiologies ("simple" vs hypothalamic) and lean controls.
Methods: Concentration (μmol/g) and proportional ratio (%) of short chain fatty acids (SCFA) were measured with Gas Chromatography and gut microbiota taxonomic composition was characterized using 454 deep sequencing of the 16S rRNA gene in faeces of 14 children with "simple" obesity, 18 patients with Prader-Willi syndrome and 19 lean controls.
Results: Although there were differences between lean and obese children, there were no significant differences between children with obesity of different aetiologies. Obese children (grouped) had significantly higher concentration of acetate and propionate compared to lean controls [Median (IQR), Acetate; Obese: 369 (182) vs Lean: 248 (167); p=0.048; Propionate; Obese: 73.2 (47.1) vs Lean: 49.7 (38.4) μmol/g dry faeces; p=0.008)] but no differences regarding their proportional ratio (%). Likewise there were no significant differences in the relative abundance of any of the 20 bacterial genera between children with obesity of different aetiology. The proportion of *Bacteroides* (4.1% vs 12.2% p< 0.012) and *Roseburia* (3.0% vs 7.7 p< 0.5) were significantly higher in obese than lean children.
Conclusions: This study does not support a role of gut microbiota in obesity and suggest that the differences in SCFA and bacterial composition observed in previous studies were more likely due to differences in dietary intake (amount and composition).

P1-d3-338 Fat Metabolism, Obesity 3

Immune cell dysregulation - contributing to the risk of the development of metabolic disease and malignancies

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Background: Adult obesity is associated with chronic low-grade inflammation and immune dysregulation. The degree to which this is present in childhood obesity is not fully established.
Objective and hypotheses: We hypothesized that childhood obesity is associated with significant immune dysregulation. The objective was to compare inflammatory and immune parameters in obese and non-obese children.
Methods: We recruited 49 participants aged 6-18 years (29 obese/ 20 non-obese) and assessed immunophenotype, cytokine profiles and MicroRNA (miR) expression.
Results: No participant had Type 2 Diabetes. The mean BMI Z scores were 3.4 for the obese and 0.18 for the non-obese. HOMA IR and fasting insulin values were markedly higher in the obese (4.8±3.5 and 149±104pmol/L) compared to the non-obese (p< 0.001). Total cholesterol concentrations in the obese were within normal range (3.93±0.71mmol/L), HDL levels were low (1.01±0.2mmol/L). There was depletion of iNKT cells, important metabolic regulators and anti-tumour responders. The anti-tumour NK and CD8+ T cells were also dysregulated in the obese cohort.
Serum concentrations of TNFα, leptin and soluble CD163 were higher in the obese cohort. TLR4 stimulation of obese peripheral blood mononuclear cells (PBMC) resulted in higher secretion of IL-1β (mean 1500 vs 2100pg/ml in obese cohort, p< 0.05), a cytokine described as pathogenic in metabolic disease.
MiR-33a and 33b contribute to the regulation of cholesterol homeostasis. We measured circulating PBMC levels and found significantly increased expression of miR-33a/33b in the obese cohort compared to non obese. There was also loss of the miR-34a, a potent tumour suppressor in the obese cohort.
Conclusions: There are major alterations in the immunophenotype, cytokine profile and miR expression in our obese cohort. The results highlight the imperative for prevention and early intervention in childhood obesity to reduce risk of metabolic disease and future malignancies.

P1-d3-339 Fat Metabolism, Obesity 3

Abdominal fat in newborns: relation to circulating long-chain poly-unsaturated fatty acids (LCPUFA)

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Background: Maternal nutrition is the sole source of long-chain polyunsaturated fatty acids (LCPUFA) in the fetal circulation.
Objective: We aimed at testing the hypothesis that neonatal body composition relates to circulating LCPUFA.
Subjects and methods: The study population consisted of 38 singleton, term newborns (18 girls, 20 boys; birthweight Z-score between -1 and +1). Body composition was assessed by absorptiometry (DXA) at postnatal ages 2 wk and 4 mo. LCPUFA profile was assessed in cord serum by gas chromatography mass spectrometer obtaining quantitative values (nmol of PUFA per g of hemoglobin) of Omega 6 [Arachidonic Acid (AA;20:4n-6) and Linoleic Acid (LA;18:2n-6)] and Omega 3 fatty acids [Eicosapentanoic Acid (EPA;20:5n-3) and Docosahexaenoic Acid (DHA; 22:6 n3)].
Results: Cord LCPUFA levels did not associate with lean mass or total fat mass at age 2 wk, but associated negatively with abdominal fat (after adjustment for birth length and birth weight): AA, r=-0.5; p=0.002; LA, r=-0.6; p=0.0004; EPA, r=-0.4; p=0.03; DHA, r=-0.5; p=0.002. None of the associations between cord LCPUFA and abdominal fat were still detectable at age 4 mo.
Conclusion: Fetuses with higher LCPUFA levels seem to partition their fat mass in a less centripetal fashion. The mechanisms underpinning this association remain to be delineated.

P1-d3-340 Fat Metabolism, Obesity 3

BDNF and *FTO* gene variants modified the response to short-term weight management in overweight and obese adolescents

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Background: Common gene variants identified by genome-wide association studies determine body weight and the development of obesity. If they also influence an individual response to the weight management programs, remains unclear.
Objective and hypotheses: We investigated the effect of eight previously reported obesity gene variants on weight loss and metabolic changes after the

short-term lifestyle intervention in overweight/obese adolescents.
Methods: Genotyping of variants in/near the genes: *TMEM18* (rs7561317), *SH2B1* (rs7498665), *KCTD15* (rs29941), *PCSK1* (rs6235), *BDNF* (rs925946, rs4923461), *MC4R* (rs17782313) and *FTO* (rs9939609) was performed in 505 Czech overweight/obese adolescents (BMI ≥90th percentile) aged 13-18 years, who undergone a 4-week supervised weight management program either in spas or in out-patient clinics. Anthropometric, biochemical parameters, body and trunk fat and blood pressure were assessed before and after the intervention.
Results: There were no differences between genotypes with regard to the baseline values of examined parameters. Boys - carriers of the *BDNF* rs4923461 obesity risk allele reduced their body weight and BMI more than non-carriers ($p < 0.05$). The greater reduction in waist circumference and in both, total and low density cholesterol was also demonstrated in girls with this variant ($p < 0.05$). Furthermore, boys carrying the risk allele of the *FTO* variant exhibited a greater decrease of BMI in comparison with non-carriers. However, the most pronounced reductions in waist and abdominal circumference and trunk fat were observed for heterozygotes ($p < 0.05$).
Conclusions: The *BDNF* rs4923461 and the *FTO* rs9939609 gene variants affected the response to the short-term weight management in Czech overweight/obese adolescents. The sex-specific effect of these variants was observed.
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P1-d3-341 Fat Metabolism, Obesity 3

Timing and body mass index at adiposity rebound are associated with metabolic risk in 7-year old children

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Background: Adiposity rebound (AR: increase in BMI after infant nadir) before age 5y has been associated with increased metabolic risk; however, the combined effect of timing of AR and BMI at AR has been less explored.
Objective: Assess the association between the timing of AR and BMI at AR on metabolic risk in 7y children. We hypothesize that a younger age at AR and higher BMI at AR are both independently associated with increased metabolic risk.
Methods: In 550 children participants of the Growth and Obesity Chilean Cohort Study, weight and height from 0 to 3y was abstracted from health records and measured by trained dietitians thereafter. BMI curves 0-7y of age were used to estimate age and BMI at AR. Early AR was defined as AR before 5y. At 7y waist circumference (WC) was measured and a blood sample was collected to analyze: glucose, insulin, and lipid profile. We built a metabolic risk score using standardized scores (SDS) of WC, glucose, insulin, triglycerides and HDL-C. For each of the metabolic outcomes we run linear regression models including timing of AR, BMI at AR, adjusted for sex, age and maternal education.
Results: The mean age of AR was 4.89 ± 1.83y in girls and 5.21 ± 1.71y in boys ($p< 0.05$); 52% of children had and early AR. Early AR was significantly associated with increased WC [β: 3.59 (95% CI: 2.74, 4.38)] and worse metabolic risk score [β: 0.24 (0.15, 0.32)]. BMI at AR was also independently associated with WC [β: 2.70 (2.47, 2.91)] and metabolic risk score [β: 0.10 (0.08, 0.13)] although effects were of smaller magnitude than those of timing of AR.
Conclusions: Earlier AR as well as increased BMI at AR predicts higher metabolic risk at 7 years children.

P1-d3-342 Fat Metabolism, Obesity 3

Miglitol increases energy expenditure by up-regulating uncoupling protein 1 (UCP1) in brown adipose tissue (BAT) of diet-induced obesity mice

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Background: Miglitol is an oral anti-diabetic drug that acts by inhibiting the breakdown of complex carbohydrates into glucose. Miglitol has recently shown to help control obesity and ameliorate insulin resistance. However, the mechanisms are not clear.
Objective: To determine whether genes related to β3 adrenergic signaling, which is known to have a role in obesity, are involved in the anti-obesity effect of miglitol.
Methods: Four-week-old male C57BL/6J diet-induced obesity mice were fed a high-fat diet alone (HF) or with a high fat diet plus miglitol (HFM). Expressions of genes and proteins related to β3-adrenergic signaling in brown adipose tissue (BAT) were analyzed. These included uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), protein kinase A (PKA), hormone sensitive lipase (HSL), and p38 α mitogen-activated protein kinase (p38αMAPK).
Results: Miglitol significantly prevented dietary-induced body weight gain with no differences in energy intake. At 8 weeks, body weight and HOMA-R value of the HFM mice (25.8±0.4g and 4.0±0.7, respectively) were significantly less than those of the HF mice (27.3±0.4g and 8.4±1.3) (both $p< 0.05$). No significant difference was observed in the levels of plasma glucagon-like peptide 1 (GLP-1). Oxygen consumption was clearly higher in HFM than HF ($p< 0.05$). Histological analysis revealed that miglitol decreased the number of lipid droplets in cells of BAT. Miglitol enhanced the protein and gene expressions of UCP1 ($p< 0.05$) and increased the protein expressions of PGC-1α, PKA, HSL, and p38αMAPK of BAT ($p< 0.05$).
Conclusions: Miglitol increased energy expenditure by upregulating UCP1 in BAT and showed an anti-obesity effect. Our results suggest that one of miglitol's effects is to stimulate β3 adrenergic signaling.

P1-d1-343 Fat Metabolism, Obesity 4

An association between markers of endothelial dysfunction and early signs of renal damage in obese children and adolescents

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Background: Obesity is associated with endothelial dysfunction, which contributes to the development of cardiovascular and renal diseases. Increased levels of inflammatory and oxidative stress markers, such as intercellular adhesion molecule 1 (ICAM-1) and myeloperoxidase (MPO), have been associated with the development of atherosclerosis. However, to date no data are available on their potential role in the pathogenesis of obesity-related renal disease.
Objective and hypotheses: To evaluate whether serum levels of ICAM-1 and MPO are increased in obese children and are associated with markers of renal function.
Methods: 80 obese children (41 boys, age: 12.0±2.8 years; BMI SDS: 2.15±0.52) and 40 normal weight peers (17 boys, age: 12.7±3.2 years, BMI SDS: -0.33±0.74) were recruited. Anthropometric measurements (height, weight, BMI) were performed and blood samples were collected for measuring ICAM-1, MPO and creatinine. A 24-hour urine collection was obtained for assessing albumin excretion rate (AER). Glomerular filtration rate (eGFR) was calculated with the Schwartz formula.
Results: ICAM-1 and MPO were significantly higher in obese than control children: ICAM-1: median(interquartile range) 0.572 (0.414-0.994) vs 0.366 (0.250-0.594) μg/ml, $P< 0.001$; MPO: 163.19 (79.84-244.37) vs 41.27 (36.77-116.02) ng/ml, $P< 0.001$. Obese children also had higher AER (mean±SD: 8.70±3.11 vs 7.50±1.94 ug/min, P=0.017) and eGFR (144.31±24.52 vs 133.36±17.16 ml/min/1.73m^2, P=0.013). BMI SDS was significantly associated with ICAM-1 (β=0.29, P=0.002), MPO (β=0.20, P=0.03), AER (β=0.26,

P=0.03) and eGFR (β=0.20, P=0.03). A significant association was also found between ICAM-1 and AER (β=0.26, P=0.005) and eGFR (β=0.22, P=0.014).
Conclusions: Obese children have increased markers of endothelial dysfunction and early signs of renal damage. ICAM-1 is related to hyperfiltration and AER, suggesting a potential role of endothelial dysfunction in the pathogenesis of obesity-related renal damage.

P1-d1-344 Fat Metabolism, Obesity 4

Abstract has been withdrawn

P1-d1-345 Fat Metabolism, Obesity 4

Impact of MTHFR genotype on HDL cholesterol in obese adolescents

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Background: Observational studies show higher total plasma homocysteine (tHcy) in patients with incident vascular disease, independent of other risk factors. The 677C→T polymorphism in methylene tetrahydrofolate reductase (MTHFR) causes higher tHcy (in TT homozygotes) and is a risk factor for vascular disease. MTHFR affects multiple metabolic processes via methylation, which may include lipid metabolism, influencing overall vascular risk.
Objective and hypotheses: We hypothesised that MTHFR affects lipids in children and aimed to determine the effect of MTHFR genotype on lipids in obese children and controls.
Methods: We studied 56 subjects with obesity (age 13.4±2.2, BMI z-score +1.7 to +3.0, 27 male) and 43 non-obese controls (14.3±3.4, 21 male). BP, height, weight, BMI (and z-scores) together with total, LDL and HDL cholesterol, triglycerides, glucose, HbA1c and tHcy were measured. MTHFR genotype was determined by PCR and RFLP analysis after digestion with *Hinf1*.
Results: HDL cholesterol was lower in obese children than controls (1.09±0.21 mmol/L vs 1.36±0.3; p=0.001). Among obese children, HDL cholesterol was significantly higher in TT homozygotes (1.28±0.24 mmol/L) than in heterozygotes (1.03±0.22) or in CC homozygotes (1.08±0.16) (ANOVA, p=0.014). There was no difference in total (p=0.92) or LDL cholesterol (p=0.74), triglycerides (p=0.54), glucose (p= 0.93) or HbA1c (p=0.54) between genotype groups in obese children. In control children, MTHFR genotype did not impact on HDL (p=0.24), or any other lipid values.
Conclusions: MTHFR genotype has effects beyond influencing tHcy and may modify vascular risk via multiple mechanisms, such as lipids, particularly in higher risk groups (eg obesity), in part explaining the variation in results of studies assessing the effect of MTHFR genotype on vascular risk and in folate intervention studies. Assessment of the impact of individual risk factors for vascular disease needs to account for multiple interacting effects.

P1-d1-346 Fat Metabolism, Obesity 4

If I say: "a small bottle of soft drink a day means 24 kg of sugar a year" do you understand? A new communication strategy for adolescent health promotion

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Background: Communication campaigns are effective in changing health behaviours. Modifying behaviours and lifestyles is a crucial factor in obesity prevention.
Objective and hypotheses: Raising adolescents' motivation in acting healthier behaviours through an experimental communication strategy (EXP).
Methods: A pragmatic trial in 2 secondary schools of a suburban area of Naples, Italy. The sample was cluster-randomised into 2 groups to whom a 1 hour educational session on obesity-related topics was given: A) 134 subjects EXP (involving the pupils in calculating, on a yearly basis, the total amount of junk foods and soft drinks ingested, and the walking distance covered in 30 minutes); B) 104 subjects using a traditional methodology (TR). A questionnaire on Knowledge, Attitude and Practice (KAP) was elaborated, tested through a pilot study, and self-administered before the intervention (T0), 3 months (T3m) and 9 months (T9m) after.
Results: The 2 groups did not differ for socio-economic status, sex, age and KAP characteristics at baseline. At T3m and T9m, positive changes in KAP were observed using EXP (p< 0,05) for:
1) Knowledge about fruit/vegetable, breakfast and water consumption;
2) Attitude towards breakfast, sedentariness and physical activity;
3) Practice of consuming breakfast, physical activity and reducing sedentariness.
Some results are shown:

QUESTION	T0-EXP	T0-TR	p	T3m-EXP	T3m-TR	p	T9m-EXP	T9m-TR	p
KNOWLEDGE. How many fruit/vegetable portions we should eat/day? (>5)	69.4	63.5	0.334	93.2	70.2	0.000	85.1	67.6	0.001
ATTITUDE. Would you wake up earlier to have breakfast? (yes)	64.2	51.0	0.243	79.1	56.7	0.000	81.3	56.7	0.000
PRACTICE.Do you usually use the stairs or you take the lift?(stairs)	44.0	49.0	0.442	61.9	47.1	0.022	58.2	42.3	0.015

[results]

Conclusions: EXP has been responsible of behavioural changes towards a healthier lifestyle in the short and medium term and can be seen a cost-effective strategy for the prevention of obesity.

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Lack of growth hormone action modifies the serum lipid profile and metabolic parameters in response to a high fat diet

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Background: GH receptor KO mice are dwarf, hypoinsulinemic, hypoglycemic, obese and have an increase in total fat mass.
Objective and hypotheses: Our aim was to investigate whether GH receptor disrupted mice (GHR KO mice) respond differently to a high fat diet (HFD) compared to wild type (WT) mice.
Methods: Male C57BL/6J wild type (WT) and GHR KO mice were weaned onto standard chow at 25 days of age. One week later, mice were divided and fed with standard chow (normal diet; ND) or HFD (60% fat) during 50 days and were then killed.
Results: At weaning, KO mice weighed less that WT mice (WT: 13.0±0.3, KO: 6.0±0.1 g; p< 0.0001). Results of metabolic parameters and serum lipid profile are summarized below.

	WT ND	WT HFD	KO ND	KO HFD	ANOVA
Change in body weight (%)	134.0 ±3.4	170.7 ±4.7*	134.5 ±3.1#	227.8 ±12.9*#&	p<0.0001
Food intake (Kcal/wk/g bw)	3.2 ±0.2	3.9 ±0.2*	4.4 ±0.1*#	4.4 ±0.1*#	p<0.0001
Change in fat mass (%)	6.9 ±0.7	13.5 ±2.1*	25.8 ±0.3*#	38.5 ±1.4*#&	p<0.0001
Glucose (mg/dl)	148.3 ±6.3	163.6 ±7.1	88.3 ±5.0*#	146.8 ±11.7&	p<0.0001
Insulin (ng/ml)	1.0 ±0.2	1.3 ±0.3	0.2 ±0.1*#	0.7 ±0.2&	p<0.003
Leptin (ng/ml)	1.0 ±0.3	4.2 ±1.6	0.8 ±0.2	5.6 ±1.2*&	p<0.0001
Total lipids (mg/dl)	666.1 ±17.2	663.9 ±27.4	558.0 ±20.1*#	608.2 ±18.9	p<0.002
NEFA (mM)	1.1 ±0.08	0.9 ±0.05	1.8 ±0.16*#	1.3 ±0.07&	p<0.0001
Totalcholesterol (mg/dl)	169.7 ±9.1	218.7 ±14.4*	144.4 ±9.2#	230.2 ±22.3*&	p<0.0005

[Table 1]
* different from WT ND, # different from KO ND, & different from KO ND.
Conclusions: Although GHR KO mice gain a higher percentage of weight and fat mass on a HFD compared to WT, serum metabolic parameters and lipid profile are similarly affected.

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Pediatric obesity and vitamin D deficiency: a proteomic approach identifies multimeric adiponectin as a key link between these conditions

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Background: Key circulating molecules that link vitamin D (VD) to pediatric obesity and its co-morbidities remain unclear.
Objectives and hypotheses: Using a proteomic approach, our objective was to identify key molecules in obese children dichotomized according to 25OH-vitamin D (25OHD) levels.
Methods: A total of 42 obese children (M/F=18/24) were divided according to their 25OHD3 levels into 25OHD3 deficient (VDD; n=18; 25OHD< 15 ng/ml) or normal subjects (NVD; n=24; >30 ng/ml). Plasma proteomic analyses by two dimensional (2D)-electrophoresis were performed at baseline in all subjects.
VDD subjects underwent a 12mo treatment with 3000 IU vitamin D3 once a week to confirm the proteomic analyses.
Results: The proteomic analyses identified 53 "spots" that differed between VDD and NVD (p< 0.05), amongst which adiponectin was identified. Adiponectin was selected for confirmational studies due to its tight association with obesity and diabetes mellitus.
Western Immunoblot (WIB) analyses of 2D-gels demonstrated a downregulation of adiponectin in VDD subjects, which was confirmed in the plasma from VDD with respect to NVD subjects (p< 0.035) and increased following 12mo vitamin D3 supplementation in VDD subjects (p< 0.02). High molecular weight (HMW) adiponectin, a surrogate indicator of insulin sensitivity, was significantly lower in VDD subjects (p< 0.02) and improved with vitamin D3 supplementation (p< 0.042).
A direct effect *in vitro* of 1α,25-(OH)2D3 on adipocyte adiponectin synthesis was demonstrated, with adiponectin and its multimeric forms upregulated, even at low pharmacological doses (10^{-9}M) of 1α,25-(OH)2D3. This upregulation was paralleled by the adiponectin interactive protein, DsbA-L, suggesting that the VD regulation of adiponectin involves post-transciptional events.
Conclusion: Using a proteomic approach, multimeric adiponectin has been identified as a key plasma protein that links VDD to pediatric obesity.

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Mutations in the leptin receptor *(LEPR)* gene in patients with early onset extreme obesity - a case series

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Background: The prevalence of homozygous mutations in the leptin receptor (*LEPR*) gene was 3% in a cohort of patients with early onset extreme obesity. 6 of the 8 affected children had consanguineous parents. Despite this report, *LEPR* mutations are not routinely tested for, and only 11 affected families are published in the literature.
Objective: Our aim is to raise awareness of this monogenetic form of obesity.
Methods: Over the past 12 months, three patients with early onset extreme obesity and mutations in the *LEPR* gene were presented to our pediatric obesity center and were gathered in a case series.
Results:
1. 34 months old boy, BMI: 40 kg/m² (+5.4 SDS). A new homozygous deletion with loss of function was identified: exon 3-20.

2. 33 months old boy, BMI 30 kg/m^2 (+4.4 SDS). Two published homozygous missense point mutations were identified: exon 8, c.9467C>A and exon 14, c.1938G>T.
3. 32 months old girl, BMI 45 kg/m^2 (+5.5 SDS). A published homozygous mutation resulting in a deleterious frame shift was identified: Exon 5, c.461dupA (p.N154Kfs*3).
All three patients had in common:
• extreme hyperphagia
• dramatic weight gain in the first 6 months of life, surpassing the 97th weight percentile between 1 and 6 months of age
• extreme obesity at the time of presentation (BMI > +4SDS)
• normal-weight, consanguineous parents of Turkish ancestry
Conclusion: Together with the high reported prevalence rate, this case series suggests that mutations in the LEPR gene are a common cause of early onset extreme obesity. If no other causes are identified, genetic testing of these patients should include sequencing of the LEPR Gene, especially when consanguinity is present.
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P1-d1-350 Fat Metabolism, Obesity 4

Efficacy, safety and tolerability of statin therapy in adolescents with familial hypercholesterolaemia

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Background: In familial hypercholesterolemia (FH), the efficacy and safety of statins (ST) show interindividual variation. Several genetic and environmental factors may contribute to this variability.
Objective: To assess efficacy, safety and tolerability of therapy with atorvastatin (A) in our cohort of FH adolescents.
Methods: 18 FH patients (14.8 ± 3.45 yrs) were started on A, after at least 6 months of TLCs diet. Their follow-up lasted 35.25 ± 37.72 months. Auxological and biochemical data were collected at: start of TLCs diet (Tb); beginning of therapy (T0); after 3 months (T1); after 1 year (T2) and at the end of follow-up (T3). Data were analyzed according to gender, type of mutation (defective vs. negative), presence of familial history of premature cardiovascular disease (CVD + vs. CVD-) and dose of A (10 vs. 20 mg/die).
Results: Lipid metabolism significantly improved during treatment with A.

	Tb	T0	T1	T2	T3
Total Cholesterol (mg/dl)	334.93 ± 62.81	322.37 ± 37.38	223.00 ± 38.18*	227.88 ± 30.68*	226.87 ± 43.35*
LDL-Cholesterol (mg/dl)	258.66 ± 55.75	241.12 ± 37.61	155.50 ± 38.90*	151.00 ± 24.76*	148.37 ± 38.63*

*[Table: * statistical significance vs. T0]*

Multivariate regression analysis identified a positive familial premature CVD as independent predictor factor for the improvement of LDL levels on A. During treatment only 2 patients (12.5%) complained transitory side effects, but in 6 patients (37.5%) A was temporarily discontinued because of increase of creatinphosphokinase (CPK). At T1 males showed a greater increase of CPK than females (p 0.02). At T3 patients on 10 mg/die showed a significantly higher CPK levels than those treated on a higher dose (p 0.05).
Conclusions: A is efficient in improving lipid metabolism in FH children and adolescents. A familial history of premature CVD may influence the therapeutic compliance and let to the achievement of a better lipid profile. Side effects, especially the increase of CPK levels, are frequent on ST, especially in males and independently from current pharmacological dose.

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Metformin prevents weight gain in youth on second generation antipsychotics

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Background: Second Generation Antipsychotics (SGA) are being used increasingly to treat children and adolescents with mental illness. While symptoms are relieved, dramatic weight gain is a frequent side effect, especially in youth. Weight gain is associated with metabolic complications (including diabetes), cardiovascular disease risk, as well as poor treatment compliance. While randomized controlled trials have shown that metformin (Met) can prevent further weight gain on SGAs, dosing and timing of treatment initiation have yet to standardized.
Objective and hypotheses: Met response will be affected by baseline patient characteristics and duration of SGA treatment.
Methods: Two groups of psychiatric inpatients were treated with Met:
Group 1 (G1, n=32, 47% female, age 13.9±2.5 [± standard deviation], 38.7% Black): on SGAs for ≥ 2 months (9.2±2.5 months, range 2.3-24.6), had Met added for either weight gain > 7% AND BMI > 85%ile;
Group 2 (G2, n= 18, age 14.5±2.2, 47% Black): started on Met within 2 weeks of SGA initiation.
Results: A larger than expected number of psychiatric inpatients (80%) gained > 7% body weight on SGAs, with 40% receiving multiple psychotropics. The BMI z-score (z) was greater at Met initiation in G2 (2.3±0.4 v 1.7±0.6). BMIz increased 0.38 in G1 prior to Met. Met stabilized BMIz in both groups, but G2 responded more quickly than G1 (G x time p = 0.002) and at a lower Met dose (764±225 v 834±285 in G1). Treatment group contributed to Met response even after controlling for baseline BMIz (p=0.002). G1 response to Met was associated with length of time on SGAs (p=0.049), a > 7% increase in weight in the 2 months prior to Met initiation (p=0.0007), and baseline BMI (p< 0.0001).
Conclusions: Dramatic weight gain occurs commonly in the controlled inpatient psychiatric setting and is abrogated by Met. Standards for Met treatment must take into account that Met response and dose are dependent on baseline BMI and how long the patient is on SGAs.

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The utility of natriuretic peptides as novel cardiovascular biomarkers in girls with Turner syndrome: comparison of findings to obese children and adolescents

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Background: Turner Syndrome (TS) is associated with increased cardiovascular mortality and morbidity. The consequent haploinsufficiency of short stature homeobox(SHOX) gene due to complete absence of one X chromosome or its terminal end has been associated with reduced concentrations of B-type natriuretic peptide(BNP).
Objective: To determine whether the novel biomarkers,BNP and atrial natriuretic peptide (ANP) are reliable in screening for cardiovascular risk (CVR) as proven in nonTS subjects
Methods: We compared demographic, anthropometric, blood pressure (BP) and laboratory related parameters of CVR, serum BNP and ANP levels, carotid ultrasound and echocardiography related parameters in61girls with TS (mean age 13.3±5yr) and 30 pubertal stage- matched obese peers.None of the subjects were receiving anti-hypertensive, and anti-diabetic drugs.
Results: TS girls had lower birth weight,body mass index (BMI) standard deviationscore (SDS), homeostasis model assessment-insulin resistance (HOMAIR), BNP and ANPlevels than obese girls(p< 0.05). TS girls had high-

er diastolic BP SDS, arterial stifness indices[β-index, Peterson elastic modulus (E_p)] than obese controls. TS girls had lower left ventricular mass (LVM), left atrial index (LAI), compliance (CC) and distensibility coefficients (DC) than obese controls. In TS girls, BNP correlated only with Awave velocity (r=0.29). In obese girls, BNP and ANP correlated significantly with BMI SDS (r=-0.52,r=-0.61), LAI (r=0.52,r=0.45), HOMA-IR (r=-0.81,r=-0.48), pubertal stage (r=0.65,r=0.39), β-index (r= 0.6,r= 0.43), E_p (r=0.49, r=0.29), Young modulus (r=0.58,r=0.54), vascular strain (r=-0.45,r=-0.33), carotid IMT (r=0.54,r=0.2), CC (r=-0.77, r=-0.4), DC (r=-0.24, r=-0.5).
Conclusions: BNP and ANP levels do not seem to be reliable screening biomarkers of cardiovascular disease in TS girls as in nonTS subjects. The inherent systemic vasculopathy and relative myocardial hypoplasia owing to TS may account for the lack of the validity of these markers.

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Adipocyte selective TSH receptor knockout mice increased susceptibility to obesity

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Background: Thyroid-stimulating hormone receptor (TSHr) expression and activity have been demonstrated in multiple tissues including white and brown adipocytes. We have previously shown that specific removal of adipocyte TSHr in mice affects adipocyte size and metabolism without affecting body weight when the animals are fed regular chow diet. The animals were otherwise healthy and had no signs of hypothyroidism and the TSHr were normally expressed in all other organs investigated.
Objective and hypotheses: In the present study, we investigated the long term impact of adipocyte selective TSHr knockout in a mouse model on body weight when fed ad libitum on either a regular chow diet (RCD) or obesity inducing diet (HFD).
Methods: At the age of 3wks animals were assigned to eight groups. HFD (60% fat, D12492l; Research Diets) to adipocyte selective TSHr knockout (KO) male (n=28) and female (n=26) and wild-type (WT) male (n=27) and female (n=30). RCD to adipocyte selective TSHr knockout male (n=25) and female (n=27) and WT male (n=26) and female (n=24). Individual body weights were recorded weekly for 40 weeks. All mice were housed on average of 3 to 4 mice per cage.
Results: A significant increase in body weight was observed in both male and female TSHr KO mice fed on RCD after 20 weeks of age. On HFD, TSHr KO mice increased weight markedly already after 4 weeks compared with all other groups. Their mean weight was 33% higher than WT controls on HFD at 15 weeks of age. WT on HFD had a significantly more pronounced weight gain than KO mice on RCD after 20 weeks. The effects were more pronounced among male animals.
Conclusions: Removal of TSHr from adipocytes results in increased weight gain in adult mice. The addition of HFD induces an increased weight in adult mice. The combination of removal of adipocyte TSHr and HFD results in a dramatic and early weight gain. Altogether, these data suggest that adipocyte TSHr plays an important role in diet-induced obesity.

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Adiposity and inflammatory markers associated with non-alcoholic fatty liver disease

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Background: Non alcoholic fatty liver disease (NAFLD) is a known morbid condition associated to obesity. Pro and antiinflammatory cytokines are strongly involved in both the physiopathology of obesity and NAFLD.
Objective and hypotheses: To evaluate the association of adiposity and inflammatory markers, with the risk of development of NAFLD in children and adolescents.
Methods: We studied 593 subjects from 2 to 18 years of age, attended in a Pediatric Nutrition Unit. Blood levels of C-reactive protein (CRP), tumor necrosis factor- α (TNF-α), adiponectin and interleukin (IL)-6 were measured. NAFLD was defined by the presence of liver steatosis in an abdominal ultrasonography and classified in three degrees (mild or I, moderate or II, severe or III). Adiposity was defined using the body mass index (BMI) according to Cole's international standard. We used SPSS v.15 for statistical analysis.
Results: 329 subjects (55.6%) were obese and 138 (23.3%) overweight. Prevalence of NAFLD was 17.8%, mainly mild forms (88.5%).NAFLD was positively related to the degree of adiposity. 100% of subjects with grade II-III of NAFLD and 66.7% with grade I were obese.CRP blood levels were significantly higher in subjects with NAFLD. Besides 22.8% of subjects with CRP >3 mg/L had NAFLD, and 33% of them were grade II-III. NAFLD was present in 15.8% of patients with CPR < 3 mg/L, but 94% of them were grade I ($p = 0.002$). When stratifying in puberal stages, this same significant association was found in prepuberal children ($p = 0.01$).No other statistically significant differences were observed when studying other inflammatory markers.
Conclusions: Children and adolescents with both high BMI and CRP blood levels are at an increased risk of developing moderate and severe forms of NAFLD. A liver ultrasound could be performed in these subjects, in order to diagnose its presence.

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Abdominal fat distribution correlates to aromatase activity in pre-school girls

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Background: We have previously shown in prepubertal males that insulin sensitivity measured by OGTT correlated to serum estradiol levels**.** Visceral adipose tissue (VAT) is known to have increased aromatase activity in adults. In short SGA girls, known to have increased risk of insulin resistance, it is found increased activity of aromatase (indirect measured as the ratio between serum estradiol and testosterone levels). Weather this is the case in healthy pre-school children with normal stature is not previously studied.
Objective and hypotheses: To study the correlation between sex steroid levels and measures of body composition.
Methods: A longitudinal study was conducted in healthy children (57 boys/48 girls) at 5 and 7 years of age, measuring hormonal status. All were prepubertal and without signs of pubarche at both timepoints. Magnetic resonance imaging (MRI) of the entire abdomen using sixteen 10 mm thick T1-weighted slices was performed in a subgroup of 48 children (30 boys/18 girls). Variables examined included waist-to-height ratio (WHtR), serum es-

tradiol-testosterone ratio with ultrasensitive methods (both modified Spectria, Orion Diagnostica, Espoo, Finland), subcutaneous adipose tissue (SAT) and VAT. The volumes of SAT and VAT were measured using semi-automated segmentation. Pearson's correlation coefficients were calculated to assess the associations between variables and a p-value of < 0.05 considered statistical significant.

Results: In 5 year old girls, low estradiol/testosterone ratio correlated to high WHtR ($r=-0.46$, $p< 0.01$) and SAT ($r=-0.43$, $p< 0.01$). Similar correlation with SAT but weeker was found in boys first at an age of 7 years ($r=-0.31$, $p< 0.05$). In both genders, there was no correlation between the estradiol/testosterone ratio and VAT (r=ns).

Conclusion: Prior to any signs of adrenarche or puberty in pre-school girls, abdominal fat distribution correlates to high testosterone levels in comparison to estradiol.

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Liver dysfunction and its association with pro- and anti-inflammatory adipokines in healthy prepubertal children with abdominal obesity

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Background: Little is known about the association between chronic inflammation and liver dysfunction/non-alcoholic fatty liver disease in childhood abdominal obesity.

Objective and hypotheses: To determine the prevalence of fatty liver among prepubertal children in relation to abdominal obesity and to analyse the association between liver function and pro-and anti-inflammatory adipokines and related SNPs.

Methods: A cross-sectional study of 168 healthy prepubertal children (78 males; mean age 8.1±1.2 years) divided into 3 groups according to their waist circumference (WC). Auxological measurements were taken. Fasting hepatic enzymes, IL-6, TNF-α and adiponectin were measured. The presence of fatty liver was determined by ultrasonography. Four SNPs located in IL-6 promoter (rs1800795), TNF-α (rs1800629) and Adiponectin (rs2241766, rs1501299) genes were genotyped.

Results: The total prevalence of fatty liver was 20.3%, increasing across the WC groups with a higher prevalence among the abdominally obese children (34.9%) compared to the normal-waist children (6.9%) and children-at-risk (7.3%) ($p< 0.001$). The hepatic fat content correlated significantly with serum ALT concentrations ($r=0.283$, $p< 0.001$). The latter were higher in the abdominally obese participants compared to their normal-waist counterparts (19.7±8.6 vs. 13.4±3.5 UI/l, $p< 0.001$) and correlated with serum concentrations of IL-6 ($r=0.238$, $p=0.015$) and TNF-α ($r=0.19$, $p=0.05$). Adiponectin levels decreased significantly with the severity of liver steatosis ($p=0.05$) and showed a negative correlation with the left hepatic lobe's size ($r=-0.248$, $p=0.011$). The latter was bigger in the TT +276 adiponectin homozygotes compared to G-carriers ($p=0.042$), while A-allele carriers of TNF-α G-308A had significantly bigger right liver lobe ($p=0.005$).

Conclusions: The present study adds to the knowledge about liver dysfunction and subclinical inflammation in abdominally obese children, pointing at possible genetic background.

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Pre-pregnant BMI is a predictor of the offspring's adult risk for overweight and obesity

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Background: The world wide epidemic of obesity continues unabated, and the pathway towards obesity is not fully understood.

Objective and hypotheses: First, to analyse what impact pre-pregnant BMI has on the risk for the next-generation to develop overweight and obesity in adulthood. Second, to study how much maternal pre-pregnant BMI has increased during one generation. We hypothesis that high pre-pregnant BMI is a risk factor for next generation adult overweight and obesity.

Methods: The investigation was performed as an intergenerational retrospective cohort study comprising women who gave birth between 1973 and 1982, and their first born whom themselves gave birth to their first infant between 2000 and 2008.

Birth characteristics of 28 321 women, and their daughters included in the Swedish Birth Register were analysed. Multiple logistic and linear regression analyses were performed.

Results: Females born of overweight mothers (BMI>25), had a two-fold (adjusted OR 2.40, 95% Cl 2.22-2.60) increased risk of being overweight (BMI>25) as adults. Further, females born of obese mothers (BMI>30) had a more than four times (adjusted OR 4.50, 95% CI 3.83-5.30) increased risk of being obese themselves, compared to individuals born of mothers with an BMI below 25. Between the two time periods 1973-1982 and 2000-2008 the prevalence of overweight and obesity during pregnancy increased from 13.8% to 21.1% and 3.0% to 11.3% respectively. During the same time period the prevalence of smoking during pregnancy decreased from 37.8% to 16.4%.

Conclusion: Pre-pregnant BMI is a predictor of next generation adult overweight and obesity. Pre-pregnant BMI has increased between the time period 1973-1983 and 2000-2008. In the debate against obesity it is necessary to stop the viscous circle of obese mothers giving birth to individuals predisposed for obesity. Interventions are needed early in life.

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A novel heterozygous splice-site mutation in two siblings with Bardet-Biedl syndrome

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Introduction: We studied two siblings with obesity and psychomotor developmental delay, referred for evaluation of possible Prader-Willi Syndrome.

Case study: The first patient is a 5 y. o. male with excessive weight gain associated with voracious appetite since the age of 6 months. Past medical history was significant for mild astigmatism. Physical exam revealed a BMI of 32.8 (+4.3 SD), prominent forehead, deep-set eyes and brachycephaly, nasal bridge, brachydactyly and descended testes with hypoplastic scrotum. His 2 y. o. sister presented with the same chief complaint but an onset of weight gain at 3 months. Her BMI was 29.2 (+5.1 SD). She had similar facial characteristics in addition to hypoplastic labia majora and minora. Both siblings had bilateral hand postaxial polydactyly repair and cognitive delays.The genetic analysis in our patients revealed 2 mutations in *BBS1* gene:

- **C**.1169t >G heterozygous missense mutation
- **C**.433-2A >G heterozygous splice-site mutation, a novel variant.

The mother had a C.1169t >G missense mutation, whereas the father had a novel C.433-2A>G mutation.

BBS is a rare cilliopathy: 1 in 140,000 to 1 in 160,000 newborns, characterized by retinal dystrophy, obesity, post-axial polydactyly, learning difficulties, hypogonadism and renal dysfunction. The diagnosis can be confirmed by sequencing of 16 known disease-causing *BBS* genes in 80% of patients.

Conclusion: Obesity, developmental delay and hypogonadism, are common features of PWS and BBS. Early onset of obesity however, is rarely seen before age 2 in PWS. An autosomal recessive condition should be suspected in the presence of two or more siblings with those clinical features and early onset obesity. Here we report for the first time a new splice site mutation in the *BBS1* gene associated with BBS.

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Manganese superoxide dismutase Ala16Val gene polymorphism in obese children with metabolic syndrome

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Background: Manganese superoxide dismutase (MnSOD) plays a key role in protecting cells against oxidative damage and regulating cellular concentrations of reactive oxygen species. The relation between obesity and serious diseases such as cardiovascular disorders and cancer and its relation with oxidative stress iare well defined. Polymorphism C47T of *MnSOD* gene results in alanine and valine substitution, which may affect MnSOD activity. The alanine allele generates 30% more active MnSOD protein than the valine form. Previously it has been shown that elderly obese patients has higher incidence to have valine allele.
Objective and hypotheses: The role of MnSOD Ala16Val gene polymorphism on cardiovascular risk factors was investigated in obese children.
Methods: A total of 100 obese children (59 girls and 41 boys, at a mean age of 12.68±2.09-year-old) and 100 children as a control group (67 girls and 33 boys, at a mean age of 12.54±2.32-year-old) were enrolled to the study. The frequencies of AA, AV and VV genotypes of *MnSOD* gene were compared between obese and control groups and it was also compared whether there are any differences between different genotypes regarding cardiovascular risk factors.
Results: Obese group had higher body mass index z-score, HOMA-IR, total cholesterol, triglycerides, LDL cholesterol, systolic and diastolic blood pressure and lower HDL cholesterol levels than controls. In obese group, AA, AV and VV genotype frequencies were 13%, 37% and 50% respectively whereas they were 13%, 43 and 44% respectively in control group. There was no statistically difference between groups regarding genotype groups (p=0,707).
Conclusions: The distribution of AA, AV and VV genotype in obese children with metabolic syndrome and control group were not statistically different and any relation could not to be demonstrated between Ala16Val polymorphism and cardiovascular risk factors.

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Influence of metformin on weight reduction and metabolic comorbidities in obese children and adolescents

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Background: Metformin is the initial drug for type 2 diabetes mellitus. Its use is approved for children above 10 years of age.
Objective and hypotheses: We aimed to evaluate the influence of metformin on weight loss and metabolic comorbidities in obese children.
Methods: Retrospective anthropometric and biochemical evaluation (oral glucose tolerance test [OGTT] and lipid profile) of 234 obese (BMI> +2 SDS) children (10-18 years), 56 treated with metformin [MET, 22.4 µg/kg/day] were studied at baseline. After 1 year 73.2% on treatment/43.3% without treatment (NO-MET) remained in the study. Insulin resistance (IR) was assessed by indexes [WBISI, HOMA] and area under the curve (AUC) of glucose and insulin in the OGTT (0.25×fasting+0.5×30'+0.75×60'+0.5×120'). Leptin, soluble leptin receptor (sOBR) and HMW-adiponectin levels were available in 14 patients in MET at both time-points.
Results: At baseline MET patients showed higher BMI and IR than NO-MET. At 1 year, BMI was similar and IR improved. MET patients showed a greater decrease in BMI-SDS (p< 0.001) and markers of IR. sOBR and HMW-adiponectin increased and leptin decreased, influenced by changing BMI.

	Baseline-MET	Baseline-NO-MET		1 year-MET	1 year-No-MET	
BMI_SDS	5.4±2.1	4.3±1.5	P<0.001	4.3±2.6	3.6±1.8	Non significant (NS)
TRIGLYCERIDES (mg/dl)	98±57	91±54	NS	89±42	84±38	NS
GLUCOSE (mg/dl)	97 ± 6	95±7	P<0.05	94±7	95±7	NS
INSULIN (mcu/ml)	24.6±16.7	18.5±7.2	P<0.05	14.8±7.4	16.6±8.2	NS
HOMA	6.0±4.0	4.32 ±1.7	P<0.001	3.4±1.8	4.5±4.9	NS
WBISI	0.65±0.34	0.88±0.34	P<0.001	1.19±0.48	0.88±0.46	P<0.05
AUC_GLUCOSE	285.4 ±45.8	249.3 ±26.9	P<0.001	253.6 ±36.9	257.2 ±35.2	NS
AUC_INSULIN	265.6 ±125.7	192.6 ±96.1	P<0.001	132.1 ±65.0	215.4 ±103.0	P<0.05
HBAIC (%)	5.6±0.3	5.5±0.3	P<0.05	5.5±0.4	5.5±0.3	NS

[Metabolic characterization of the studied groups]

Conclusions: Metformin treatment in obese children is associated with more extensive weight reduction and further improvement of IR.

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Toward early protection against endocrine-metabolic complications of later obesity: breastfed, large-for-gestational-age infants from non-diabetic mothers are more sensitive to insulin and gain more lean mass and less fat mass across infancy

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Background: Breastfed (BRF) large-for-gestational-age (LGA) infants from non-diabetic mothers (NDM) are partially protected from the endocrine-metabolic complications of obesity.
Objective and hypotheses: We aimed to gain insight into the early mechanisms conferring such protection.
Methods: Longitudinally (at birth, at 4 and 12 mo) we studied the body composition (by absorptiometry) and the endocrinology (fasting insulin, IGF-I) of NDM-BRF infants born LGA *vs* born appropriate-for-gestational-age (AGA).
Results: At birth, the mean Z-scores of lean mass, fat mass and bone mineral content (BMC) in the LGA infants were all between +1 and +2 (results in AGA controls were used as norms). Between 0-12 mo, AGA and LGA infants gained length and weight similarly, but LGA infants gained a mean 0.9 Kg more lean mass and 0.7 Kg less fat (and also less BMC), so that their fat-to-lean ratio evolved from an adipose level (Z-score +1) to a lean level (Z-score -1), while their fasting insulin and IGF-I levels were lower.
Conclusions: The prenatal weight gain of NDM-LGA-BRF infants is rapid but normally partitioned, whereas their postnatal weight gain has a normal rate but favours lean mass and is accompanied by a high sensitivity to insulin and perhaps to IGF-I. This sequence of weight partitioning may be one of the early-life mechanisms whereby NDM-LGA-BRF infants protect - or "vaccinate " - themselves against the endocrine and metabolic complications of obesity.

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Dyslipidaemia in survivors of childhood acute lymphoblastic leukaemia (ALL) post bone marrow transplantation and total body irradiation (BMT/TBI) is associated with abnormal differential fat deposition and adipocytokine levels

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Background: Childhood ALL survivors post BMT&TBI have high metabolic risks but the mechanisms are unclear.
Objectives: To investigate dyslipidaemia, adipocytokines and differential fat deposition in childhood ALL survivors.
Method: Childhood ALL survivors,
Group1 treated with BMT&TBI(10-14.4Gy) at median age 9.3(1.0-10.8) y(n=21,11M),
Group2 chemotherapy only (n=31,13M) were compared with
Group3 simple obesity (n=30,10M).
All were 16-26y and had:1)Fasting High-Density-Lipoprotein(HDL), Triglycerides(TG); 2)DEXA:total fat mass(FM), %; 3)Abdominal MRI: Subcutaneous, visceral, intramuscular fat%; 4)Adipocytokines: Leptin, Adiponectin, Omentin, Visfatin. Analysis: Odds ratios, ANOVA, multiple regression, Pearson's correlations at 5% significance.
Results: (Table) Group 1 showed higher prevalence of raised TG than groups 2&3[48% vs10%(OR:8.2,CI:1.9-35.5) &13%(5.9,1.5-23) respectively] and reduced HDL than group 2[55% vs27%(3.7,1.1-12)]. Group1(vs 3) showed higher visceral & intramuscular fat%, and lower subcutaneous fat%. Group1 had higher Leptin/FM and lower Adiponectin/FM than group2. Omentin and Visfatin showed no group differences. Leptin, Omentin, Visfatin correlated with all fat subtypes. Adiponectin correlated negatively but only with visceral fat(r=-0.36,p=0.004) and, negatively with time post TBI(r=-0.59,p < 0.005). Adiponectin/Visceral fat was lower in group 1[3.1(2.5-3.8)] vs 2[5.8(4.9-6.8),p< 0.001] &3[4.5(3.7-5.4),p=0.008].

Variable [mean(SD)* or geometric mean(ranges)**]	Group 1 (n=21)	Group 2 (n=31)	Group 3 (n=30)	1 vs 2 (p)	1 vs 3 (p)	**2 vs 3 (p)**
DEXA Total fat (%)*	32.9 (12.4)	35.3 (11.5)	48.2 (5.8)	0.72	<0.001	<0.001
MRI Subcutaneous fat (%) *	37.9 (12.7)	45.5 (13.0)	59.5 (4.9)	0.07	<0.001	<0.001
MRI Visceral fat (%) *	15.5 (6.2)	12.1 (4.9)	11.7 (2.6)	0.06	0.04	0.95
MRI Intramuscular Fat % *	4.8(1.6)	2.9(0.8)	3.1(1.0)	<0.001	<0.001	0.73
Leptin per total fat mass **	40.0 (24.2-66.1)	19.1 (13.9-26.4)	29.9 (13.7-65.2)	0.016	0.54	0.29
Adiponectin per total fat mass**	3.0 (2.4-3.8)	5.9 (5.0-7.1)	4.5 (3.4-5.9)	<0.001	0.06	0.11

[Total & Differential Fat, and Adipocytokine levels]

Conclusions: Dyslipidaemia in BMT/TBI survivors was associated with increased intramuscular and visceral, but reduced subcutaneous, fat. Adiponectin is a more specific marker of visceral fat.

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Quantitative MRI - not ALT- allows for early diagnosis of hepatic steatosis

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Background: The prevalence of non-alcoholic fatty liver disease (NAFLD) is up to 38% in overweight children and is anticipated to be the leading cause of liver failure and transplant. Early identification of NAFLD, currently based on ALT, is important for prevention and intervention.
Objective and hypotheses: We hypothesized that quantitative MR (PDFF) is a more sensitive indicator of NAFLD than BMI & ALT and aimed to compare PDFF to ALT for diagnosis of NAFLD & associated metabolic disease.
Methods: Cross-sectional study of 131 females(11-21yrs; mean 13.3±2), Race: 64% Caucasian, 31% African American & 5% Asian; Ethnicity: 27% Hispanic, 73% Non-Hispanic. Fifty-five percent of subjects had a BMI >85%. Fasting glucose, insulin, ALT, BMI, & waist circumference (WC) were measured. Hepatic fat quantified by MR proton density fat fraction (PDFF). Hepatic steatosis (HS) defined as PDFF >5.6%.
Results: Overall mean ALT was 24±13 & normal (≤40U/L) in 93% of all subjects & 70% of girls with HS. HS was found in 27% of overweight subjects & 1 subject with a BMI < 85%. Table shows correlation of metabolic markers & PDFF.

Correlation Comparison with MR PDFF

		Overweight Subjects n=75		
	All Subjects n=131	Hepatic Steatosis n=20	No Hepatic Steatosis n=55	r-value Comparison
	r	r	r	p-value
BMI	0.46*	NS	NS	NS
WC	0.45*	NS	NS	NS
ALT	0.24*	0.81*	NS	<0.001
HOMA-IR	0.41*	0.75*	NS	<0.01

[Table 1: Spearman rank correlation (r) with PDFF shows strong association of ALT and HOMA-IR but not BMI in HS. Comparison of correlations shows no difference in BMI and WC in subjects with and without HS.
**p <0.01; NS = not significant]*

Conclusions: Quantitative MRI allows early identification of HS and correlates with insulin resistance. In contrast, elevated BMI and ALT were not predictive of HS in the overweight girls. The strong correlation of ALT with PDFF in HS subjects suggests hepatocellular injury. However, 14 HS subjects had an ALT ≤40U/L and would be missed by current ALT based screening. Using an ALT of ≤16U/L rules out most HS but decreases specificity. An algorithmic approach incorporating PDFF would enhance early diagnosis of NAFLD, allowing for early prevention and intervention.

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Association of cardiac changes with serum adiponectin and resistin levels in obese children

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Background: To investigate serum adiponectin and resistin levels and their relationship with insulin resistance and cardiac changes in obese children.
Objective and hypotheses: To investigate of association of cardiac changes with serum adiponectin and resistin levels in obese children.
Methods: Ninetyfive obese and 40 healthy children and adolescent were selected for the study.Height, weight, BMISDS values were obtained for each individual. Left ventricular (LV) wall thickness, LV mass, stroke volume,cardiac output, sistolic and diastolic functions of the LV were measured using M-mode ,two dimentional color-coded echocardiography device. Serum insulin, c-peptide, triglyceride, cholesterol (LDL-c, VLDL-c, HDL-c), adiponectin and resistin levels were measured by ELISA. HOMA-IR values were calculated for each subject.
Results: Cholesterol, LDL-c, HOMA-IR values were higher in obese children than those of controls (p< 0.01). Adiponectin and resistin levels were lower than controls (p< 0.01), and these adipocity hormones were inversely correlated with HOMA-IR. Echocardiographic evaluation showed diastolic dysfunction, increased LV wall thickness and LV mass in obese children. We also detected a significant positive correlation among LV mass and resistin level, and resistin level was determined as an independent predictor of LV mass in obese children.

Conclusions: In this study, even in asymptomatic obese children cardiac structural and functional changes such as increased LV mass, diastolic dysfunction were demonstrated. Although decreased adiponectin level was not related to cardiac changes, it was shown that decreased resistin level lead to LV hypertrophy.

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Low omentin-1 levels are related with clinical and metabolic parameters in obese children

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Objective: This is the first clinical study evaluating the relation of serum omentin 1 levels with anthropometric and metabolic parameters in obese children with a particular interest to identify the possible role of omentin 1 in childhood obesity and related metabolic disturbances.
Subjects-methods: The study included obese children with a body mass index (BMI) >95th percentile and healthy children with a BMI < 85th percentile. The healthy and obese subjects had similar age and gender distribution. Glucose, insulin, lipid profile, and omentin 1 levels were measured to evaluate the metabolic parameters.
Results: Forty-nine obese children who applied to our department with complaint of weight gain and 30 healthy age and sex matched subjects were enrolled. In obese children BMI, body mass index-standard deviation score (BMI-SDS), systolic blood pressure (SBP), diastolic blood pressure (DBP), mid-arm circumference (MAC), triceps skin fold (TSF), waist circumference (WC), homeostasis model assessment-insulin resistance (HOMA-IR), serum insulin, and triglyceride levels were higher whereas omentin-1 levels were lower than control subjects ($p< 0.05$). In the obese group, omentin 1 level was negatively correlated with BMI, insulin , HOMA-IR, and WC, while no significant correlation was observed with other parameters ($p>0.05$). Additionally, although statistically insignificant, patients with IR (n=31) had lower omentin-1 levels compared to obese children without IR (n=18).
Conclusion: Our data indicates that serum omentin 1 levels are
i) lower in obese children and
ii) negatively correlated with BMI, WC, HOMA-IR and insulin levels suggesting that omentin 1 might be a biomarker for metabolic dysfunction also in childhood and adolescence.

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An age-dependent association between a single nucleotide polymorphism in the MC4R gene and adiposity indexes in a population of Caucasian school-children

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Background: Genome-wide association studies have led to the identification of many single nucleotide polymorphisms (SNPs) associated with obesity. Interestingly, some SNPs (MC4R and FTO genes) seem to have an age-dependent effect on obesity risk.
Objective and hypothesis: To assess whether the rs12970134 variant in the MC4R gene is associated with BMI and waist circumference (WC) in a genetically homogeneous population of Caucasian school-children and whether these associations vary with age.
Methods: 745 school-children (353 boys, age: 8.3±1.4 (range 5.7-11.8) years) underwent anthropometric assessments (height, weight, BMI, WC). According to BMI, children were divided in: normal weight (< 85th percentile), overweight (85-95th percentile), obese (>95th percentile). DNA was extracted from saliva samples.
Results: Out of the 745 children, 138 (18.5%) and 106 (14.2%) were overweight and obese, respectively. The frequency of the rs12970134 AA risk genotype was significantly higher in subjects with a BMI>85th (8.3%) than in those with a BMI< 85th percentile (3.0%), P=0.001. BMI SDS and WC SDS progressively increased across the rs12970134 genotypes (GG vs AG vs AA): BMI SDS: 0.40±1.06 vs 0.51±1.10 vs 1.00±0.88, P=0.004; WC SDS: 1.10±1.24 vs 1.24±1.23 vs 1.69±1.05, P=0.01.
The rs12970134 SNP was significantly associated with BMI SDS (B[95%C.I]: 0.194[0.061-0.326], P=0.004) and WC SDS (0.207[0.051-0.392], P=0.009). After dividing the study population in tertiles of age (< 7.5; 7.5-9, >9 yrs), a stronger association was documented in children in the lower and upper tertiles: < 7.5yr, BMI SDS: 0.353[0.122-0.585], P=0.003; WC SDS 0.35[0.07-0.63], P=0.01; >9yr: BMI SDS: 0.312[0.081-0.543], P=0.008), WC SDS: 0.14[0.08-0.61], P=0.01.
Conclusions: In pre-pubertal children, the rs12970134 MC4R variant is associated with adiposity indexes. Of note, the effect of this SNP appears to be age-dependent, suggesting a relevant role of timely preventive interventions in young subjects.

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Liver transplantation as a successful therapy in a patient with homozygous familial hypercholesterolaemia - long-term follow up

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Introduction: Homozygous familial hypercholesterolemia (HFH) is rare inherited disorder, leading to severe atherosclerosis and early cardiovascular death if untreated. Since medications do not reduce cholesterol levels satisfactorily, LDL apheresis is a mainstay of its management. However, liver transplantation (LT) was also shown to be a possible treatment option.
Case report: A boy aged 4.5 years was referred because of xantomas. Extremely high values of total (24.8 mmol/L) and LDL cholesterol (21.6 mmol/L) were detected. The homozygous mutation *LDRL* c.1754T>C (p.Ile585Thr) was found.
Despite highly restrictive diet and bile acid sequestrants, only 25% decrease in cholesterol levels was reached. Since the age of 5, LDL apheresis was performed bi-weekly, but was interrupted for few years because of psychological problems. In meantime, the patient was receiving simvastatin and probucol. Increased IMT of carotis communis and femoral arteries was measured. LDL apheresis was restarted along with atorvastatin. At the age of 12 years the aortic valvular stenosis and mild aortic regurgitation, with increase in the left ventricular outflow tract gradient was observed.
At the age of 16 years, the patient successfully underwent deceased-donor ortopic LT. The immunosuppression regimen consisted of tacrolimus and methylprednisolone. An episode of acute rejection 2 years after LT was successfully treated with steroids. Later on, he has been maintained on tacrolimus only. Nine years after the LT his lipid levels are in normal range, cutaneous xanthomas have completely resolved and IMT is normal (0.6 mm) with hemodinamically unimportant atherosclerotic lesions in both aortic bulbs.
Conclusions: Only few LT in children with HFH have been reported. Our long-term follow up suggested that LT in HFH adolescent was a safe and effective method, definitively decreasing cholesterol levels, thus preventing the development of atherosclerosis and also increasing patient's quality of life.

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PI3K/mTOR signalling and IGFBP2 production in human adipocyte models

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Background: IGFBP2 (IGF-binding protein 2) is considered a marker for the status of PTEN (phosphatase and tensin homologue) and activity of the PI3K (phosphatidylinositol-3 kinase) /mTOR (mammalian target of rapamycin) pathway.
Objective: We evaluated IGFBP2 serum levels in a patient with a heterozygous germline *PTEN* deletion and PTEN-Hamartoma-Tumor-Syndrome (PHTS) who received an individual treatment with rapamycin. Moreover, we wanted to analyse the influence of pharmacological inhibitors of the AKT/PI3K/mTOR pathway on IGFBP2 production during adipose differentiation.
Methods: Levels of IGFBP2 were measured by ELISA in serum samples taken from the patient at every consultation. Preadipocyte cultures established from a resected lipoma of the patient and human control preadipocytes were differentiated *in vitro* and treated with inhibitors.
Results: Elevated serum IGFBP2 levels were observed in the patient with PHTS. During rapamycin treatment IGFBP2 serum levels alternated but did not decrease significantly. IGFBP2 mRNA and protein expression as well as secretion was detected in all analysed human adipocyte models during differentiation. PTEN-deficient lipoma cells were found to produce IGFBP2 during *in vitro* differentiation in comparable amounts to the non-PTEN-deficient adipocyte models (4.6±3.6 ng/ml vs. 4.1± 2.9 ng/ml secreted from SGBS cells on day 4 of differentiation). Incubation with the AKT inhibitor perifosine or the PI3K inhibitor wortmannin caused a significant decrease in both IGFBP2 expression (5μM perifosine, 100 μM wortmannin $p< 0.05$) and secretion (25 μM perifosine, 10μM wortmannin $p< 0.05$). The mTOR complex 1 inhibitor rapamycin or PD98059, an inhibitor of ERK1/2, had no significant effect on IGFBP2 production.
Conclusion: IGFBP2 expression and secretion in the lipoma cell strain seem not to be influenced by PTEN deficiency or inhibition of mTOR. Inhibition of PI3K or AKT decreased IGFBP2 expression and secretion in lipoma cells.

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Serum uric acid levels and albuminuria-to-creatininuria ratio in obese children are associated with obesity comorbidities

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Background: Elevated serum uric acid (SUA) is common in subjects with metabolic and cardiovascular diseases, but is not considered a risk factor by all. Some studies have shown that elevated SUA is associated with microalbuminuria which conversely is a proved cardiovascular risk factor. Few data on childhood obesity are present.
Methods: 430 obese subjects (age, mean±SD: 10.7±3.2 yrs) were recruited. Pathological cut offs for SUA and ACR were considered at 5.5 mg/dl, and 30 mg/g, respectively. Because no accordance on SUA distribution in childhood exists, SUA was also categorized in quartiles. Altered glucose levels according to ADA criteria, systolic (SBP) and diastolic blood pressure (DBP) > 90° percentiles, HDL-cholesterol (HDL) < 40 mg/dl (males) or < 50 mg/dl (females), and triglycerides > 150 mg/dl were considered for metabolic alterations. Glucose and insulin levels during an oral glucose tolerance test (OGTT), and HOMA-IR were also evaluated.
Results: Obese children with altered glucose levels had higher ACR ($p< 0.03$), but similar SUA levels, respect to those euglycemic. Subjects with higher SBP or DBP, or lower HDL had higher SUA levels ($p< 0.0001$ for both) but similar ACR respect to those normal. Being positive for ACR increased the risk to have altered glucose levels (OR: 6.821, IC95% 1.325-35.104; $p< 0.02$) also when corrected for age, sex, and BMI. Being in the highest quartiles of SUA increased the risk to have hypertension (OR: 1.860, IC95% 1.026-3.370; $p< 0.04$) and low HDL levels (OR: 1.917, IC95% 1.079-3.757; $p< 0.05$) also when corrected for covariates.
Fasting insulin, insulin during OGTT, were positively and independently predicted by SUA, but not by ACR.
Conclusion: Serum acid uric and albuminuria-to-creatininuria ratio are already increased in obese children and adolescents. They may predict different metabolic alterations in childhood obesity. Further studies are needed to understand their clinical significance in this age.

P1-d3-370 Fat Metabolism, Obesity 6

Early identification of impaired renal function in obese children with non-alcoholic fatty liver disease

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Objective: To early identify the impaired renal function in the obese children with non-alcoholic fatty liver disease (NAFLD).
Methods: Three hundred and eighty-six obese children were enrolled and were divided into NAFLD group and simple obesity group (control group) according to the diagnostic criteria. Clinical biochemical parameters and early impaired renal functions were evaluated and compared. Further more, we subdivided 234 obese children with age over ten years into three groups: NAFLD combined with metabolic syndrome (NAFLD+MS) group, NAFLD group and simple obesity group (control group) to take the above indexes into comparison.
Results: The urinary microalbumin of NAFLD group, NAFLD+MS group (over 10 years old), NAFLD group (over10 years old) are significantly higher than that of control which indicated that there existed early renal dysfunction in children with NAFLD and those accompanied with MS as well. Additionally, the positive correlation between urinary microalbumin and systolic pressure, triglyceride and 2h-postprandial blood glucose were found, which demonstrated the role of hypertension, glucose-lipid metabolic disorder in the pathogenesis of early impaired renal function and chronic kidney disease (CKD).
Conclusions: NAFLD are not only an early sign of early impaired renal function but also an early stage of CKD in obese children. And their occurrence and development are significantly associated with hypertension, glucose-lipid metabolic disorder. As a result, early diagnosis and treatment of NAFLD is crucial for CKD prevention.

P1-d3-371 Fat Metabolism, Obesity 6

Predictive factors for insulin resistance in children

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Background: Puberty as a rapid growth period can influence insulin resistance (IR) and type 2 diabetes risk factors.
Objective and hypotheses: To evaluate body composition (BC) and IR changes in relation to frequencies of Insulin gene (INSG) genotype rates throughout puberty in lean (control (C, n=578)) and obese (O, n=204) children.
Methods: Children were divided into groups: prepubertal O (O1) m/f n=178/117 and C (C1) n=51/46, early puberty (O2) n=67/41 and (C2) n=16/17, late puberty (O3) n=88/87 and (C3) n=14/60). 237 obese (144/129) and 259 (55/104) lean subjects were genotyped in INSG (A23HphIT polymorphism). Insulin level by radioimmunoassay technique, blood glucose, BMI, BC by dual-energy X-ray absorptiometry, HOMA-IR and Quantitative insulin check (QUICKI) indexes were evaluated.

Results: Insulin, HOMA-IR and QUICKI in O children ranges were increased as compared with C despite the pubertal stage: p=0.0001 in groups 1, p=0.001 and p=0.05 in the 2nd and 3rd ones (p=0.0001, p=0.001, p=0.003) respectively. Correlations between insulinemia, HOMA-IR and QUICKI indexes and BMI (r=0.4, 0.3 and 0.3 respectively, p=0.0001) and were revealed. These IR markers similar correlated with Android/Ginoid fat ratio (0.3, p=0.01), total fat mass (0.3, p=0.001) and weakly with lean mass (0.2, p=0.03). There were gender differences (hi-square 6.56; p< 0.05) between genotypes rates occurrence in O children: m/f=61.8%/51.9% had AA-genotype and 4.9%/13.2% - TT, versus to C children: AA-genotype - 56.4%/61.5%, TT-genotype - 5.5%/3.8% (p>0,05). Insulin, HOMA-IR and QUICKI levels was higher in AA homozygous O children respecting to TT-genotype (p=0.004, 0.006 and 0.009 in order). Insulin values were the same in lean children with AA and TT polymorphisms.
Conclusion: IR indexes influenced body fat distribution in children. A-23HphIT INSG in obese girls were significant differed from control irrespective of gender. IR markers in obese children were linked to A-23HphIT INS polymorphisms.

P1-d3-372 Fat Metabolism, Obesity 6

Early menarche and cardiovascular risk in Chilean adolescents of low- to mid-socioeconomic level

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Background: Overweight during childhood is associated with early pubertal development, mostly in females. On the other hand, early menarche is associated with higher cardiovascular risk (CVR) in adulthood.
Aim: We examined the association between age of menarche and CVR profile, and we assessed the relationship between early menarche (EM) and Metabolic Syndrome (MetS), after controlling for potential confounders.
Methods: In 388 female adolescents (16.8±0.2 years old) of Low- to Mid-SES from a longitudinal follow-up we evaluated growth (BMI and Height z-score at 5,10 and 16 years old) and waist circumference (WC), systolic and diastolic blood pressure (SBP and DBP), triglycerides (TG), high density lipoprotein (HDL-chol), and Glucose (Glu) at 16 years old. Obesity (BMI≥p95th) was diagnosed using CDC/NCHS 2000. Metabolic Syndrome (MetS) and CVR factors were diagnosed using Cook criteria: WC, SBP and DBP (≥p90), TG (≥110 mg/dl), HDL-chol (≤40 mg/dl) and Glu (≥100 mg/dl). To diagnose early menarche (EM) 25th percentile (≤11.7 y) was used. Associations were tested using ANOVA and Chi² (Pearson). Logistic regressions assessed the relation between MetS (outcome) and EM (exposure).
Results: Adolescents with EM showed significantly higher BMI and WC, as well as significantly higher prevalence of obesity, abdominal obesity and elevated SBP. Similarly, they had significantly higher prevalence of obesity at 5y, and tall stature (height z-score ≥1 DE). In different models, obesity at 5y and tall stature at 10y significantly increase the odds of early menarche. The relation between EM and Mets was insignificant, however, obesity at 5y and tall stature at 10y were both significantly associated with MetS.
Conclusions: Our findings suggest that both EM and CVR result from early onset overweight.
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P1-d3-373 Fat Metabolism, Obesity 6

Melatonin secretion in obese prepubertal patients and its correlation with metabolic syndrome and other cardiovascular risk factors

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Background: It has been suggested that, from early stages of life, among the neuroendocrine factors associated with metabolic syndrome disorders, melatonin might play an important role.
Objective: To correlate melatonin secretion with different components of metabolic syndrome and other cardiovascular risk factors in children.
Patients and methods: We evaluated 59 obese prepubertal patients (39 males: 5-12.2 years and 20 females: 5-10.4 years), with BMI >2SDS. Metabolic syndrome was defined using Cook criteria. We measured urinary *6-sulfatoxymelatonin* (6-SM) (radioimmunoassay, Stockgrand Ltd, Guildford, UK) in nocturnal (6-SMn: 6PM to 8AM) and diurnal samples (6-SMd: 8AM to 6PM). Levels of 6-SM were expressed as µg excreted per time interval and delta 6-SM as the difference between nighttime and daytime values. Insulin was measured by ECLIA (cobas E411, Roche Diagnostics GmbH. Mannheim).
Results: (median):

	6-SMn (µg)	6-SMd (µg)	**Δ 6-SM** (µg)	Insulin (µU/L)	Glucose (mg/dl)	T-Chol (mg/dl)	HDL (mg/dl)	Triglyc (mg/dl)	Uric Acid (mg/dl)
Males	2.01	0.54*	1.46	15.4	91	171.5	40.0*	99	3.99
Females	2.66	0.54	1.95	11.8	89	161.5	41.5	109	3.66

[table 1]
* Rs=0.36, p=0.0245 (Spearman Rank order correlation)

No associations were found between melatonin secretion and the presence of abdominal obesity, hypertension, metabolic syndrome or family history of cardiovascular risk in either gender.
Conclusions: In girls, no association was found in any of the clinical-biochemical variables evaluated, while in males, an association was found between 6-SMd and HDL.
The results obtained in this preliminary study would suggest the absence of an association between melatonin secretion and metabolic syndrome components in prepubertal patients. The only significant finding observed might be an incidental finding, and it would not allow for the development of predictive models at his stage.

P1-d3-374 Fat Metabolism, Obesity 6

Influence of prepubertal adiposity, insulin resistance and asymmetric dimethylarginine on blood pressure during puberty in obese subjects

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Background: Hypertension is an important cardiovascular complication of obesity, even during childhood. In addition, the persistence of abnormal blood pressure (BP) is considered a risk factor for cardiovascular events later in life. Few data are available on potential factors influencing BP changes from childhood to adolescence.
Objective and hypotheses: To assess changes in BP from childhood to adolescence in obese children and their association with BMI, insulin resistance (IR) and asymmetric dimethylarginine (ADMA).
Methods: Thirty obese children underwent a first assessment when they were prepubertal (visit 1, age: 9.0±1.2 years) and were re-evaluated during puberty (visit 2, age: 15.1±1.4 years). At both study visits anthropometric parameters were assessed, fasting blood samples were collected for measurement of

insulin, glucose and ADMA and a 24-hour BP monitoring was performed. HOMA-IR was used as an index of IR.
Results: At visit 2 the study population presented increased fasting insulin (22.7±6.6 vs 13.2±5.2 µU/ml, p=0.007), HOMA-IR (3.8±1.8 vs 2.6±1.3, p=0.005), ADMA (1.49±0.86 vs 0.67±0.38, p= 0.0001), 24-hour systolic BP (SBP) SDS (0.88±0.68 vs 0.38±0.70, p=0.0002) and diastolic BP (DBP) SDS (0.02±0.50 vs -0.47±0.82, p=0.003) compared to visit 1. At both study visits, BMI SDS, HOMA-IR and ADMA were significantly associated with 24-hour BP.

	Visit 1			Visit 2	
	24-hour SBP SDS	24-hour DBP SDS		24-hour SBP SDS	24-hour DBP SDS
BMI SDS	r= 0.45 p=0.014	r= 0.50 p=0.004	BMI SDS	r= 0.45 p=0.013	r= 0.35 p=0.05
HOMA-IR	r= 0.57 p=0.001	r= 0.32 p=0.07	HOMA-IR	r= 0.57 p=0.007	r= 0.43 p=0.017
ADMA	r= 0.63 p=0.0001	r= 0.51 p=0.004	ADMA	r=0.61 p=0.0003	r= 0.43 p=0.016

[Factors associated with BP]

In addition, overtime changes in IR and ADMA independently predicted SBP (β=0.505, p=0.002 and β=0.352, p=0.022) and DBP (β=0.605, p=0.02 and β=0.352, p=0.032) during adolescence.
Conclusions: In obese subjects BP was directly influenced by BMI, IR and ADMA both during childhood and adolescence. Of note, overtime changes in IR and ADMA predicted BP during adolescence.

P1-d3-375 Fat Metabolism, Obesity 6

Effect of pre-pregnancy BMI and gestational weight gain on the timing of adiposity rebound

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Background: Adiposity rebound (AR= increase in BMI after infant nadir) before 5y of age has been linked to increased risk of obesity and metabolic diseases. The determinants of the timing of AR are unknown. There is increasing evidence that prenatal nutrition influence postnatal growth trajectories.
Objective: To assess the effect of Pre-Pregnancy BMI and gestational weight gain (GWG) on the timing of AR. We hypothesize that Pre-Pregnancy obesity and increased GWG will be related to an earlier AR.
Methods: 547 mothers (non-diabetic nor underweight) participants of the Growth and Obesity Chilean Cohort Study, self-reported their weight at the beginning and at the end of pregnancy. In children, weight and height from 0 to 3y was abstracted from health records and measured by trained dietitians thereafter. BMI curves 0-7y of age were used to estimate age at AR. Pre-Gestational BMI was categorized as normal weight (18.5-24.9kg/m2), overweight (25-30kg/m2), or obese (>30kg/m2); GWG was classified as less than, equal to, or greater than current Institute of Medicine(IOM) guidelines. Early AR was defined as before 5y of age. Associations were tested using logistic regression models adjusting for sex, maternal education, parity and maternal smoking.
Results: 1/3 women had excess weight before pregnancy (27.2% overweight, 10.2% obesity). Mean gestational weight gain was 12.3kg and 34.2% exceeded IOM recommendations. Almost half of the children had an early AR (44.5%). Pre-pregnancy BMI and gestational weight gain were unrelated to earlier AR. **Conclusions:** Our preliminary analyses suggest that the timing of AR is not dependent on the maternal nutritional status previous or during pregnancy. Although, it's important to test whether these findings hold true for all women (testing potential interactions) these results suggest that other variables, probably birth weight and postnatal factors such as early rapid growth are related to timing of AR.

P1-d3-376 Fat Metabolism, Obesity 6

Growth restraint before birth, weight catch-up in infancy, and central adiposity in childhood: a placebo-controlled pilot study of early metformin intervention

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Background: Children born small-for-gestational-age (SGA) who develop rapid weight gain postnatally are at risk for becoming centrally adipose and insulin resistant before puberty.
Objective: We tested whether prepubertal intervention with metformin reduces total, abdominal and visceral adiposity.
Subjects and methods: We are performing a placebo-controlled pilot study in prepubertal SGA children (age 6-9 yr) with spontaneous catch-up of height (>P25) and weight (BMI P75-97), with a high amount of visceral fat (>P75, by MRI) and with high levels of circulating IGF-I (>P75). Children are randomly allocated to receive either placebo or metformin (425 mg/d) daily.
Results: In March 2013, only 6-mo results from 18 children are available; the clinical investigators remain blinded to treatment allocation, but the unblinded study statistician observed that metformin-treated children gained on average 1.4 kg less fat than placebo-treated children (P=0.03), including 0.3 kg less abdominal fat (P=0.04). So far, there are no detectable differences in growth velocity, HOMA-IR, circulating lipids, visceral fat or carotid intima-media thickness; intake of placebo or metformin does not appear to be associated with side effects; hepatic and renal safety markers remain stable in both subgroups.
Conclusion: The present results were obtained in a small study population and over a short timespan, but they provide placebo-controlled evidence that prepubertal intervention with metformin can reduce the central adiposity of SGA children whose spontaneous catch-up growth is followed by upper-quarter values for BMI (limited here to P97), visceral fat and circulating IGF-I.

P1-d3-377 Fat Metabolism, Obesity 6

C242T polymorphims in p22phox in normotensive and hypertensive children and its relation with vascular inflammatory markers

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Background: The reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidases are the main source of superoxide in phagocytic and vascular cells. The C242T polymorphism of p22phox gene (rs4673) has been linked with vascular NADPH oxidase activity in atherosclerosis and hypertension in adults.
Objective and hypotheses: To investigated the association of the C242T polymorphism with vascular inflammatory markers in normotensive and hypertensive children.
Methods: Study in a sample 114 children (32 hypertensive patients and 82 normotensive, 4-18 years). There were calculated systolic blood pressure index (SBP) and diastolic pressure index (DBP), BMI and Waist to Height ratio (W/H). It was determinate hsCRP, PAI-1, MDA and Adiponectin as vascular inflammatory markers. We determinate CYBA polymorphisms by restriction fragment length polymorphism (RFLP) and a sample of DNA of 20 patient was secuenciated. Data were expressed as interquartile range [Q1-Q3], statistical comparisons was done by Mann-Whihney and spearman correlation.
Results: The prevalence of the C allele frecuency was 0.64 and there were no differences between normotensive and hypertensive patients. There were no differences in inflammatory markers between CC group vs CT/TT (hsCRP 3.1 [0.2-12.7] vs 2.2 [0.2-9.6] mg/L, Adiponectin 12.3 [2.8-23.6] vs 13.0 [2.4-24] ug/ml, PAI 24.9 [3.7-5] vs 19.5 [4.9-40.2] and MDA 0.3 [0.1-0.6] vs 0.4 [0.2-0.7] p=NS) . In the CC group there were a positive correlation between the inflammatory marker hsCRP and SBPindex, (R=0.5 p< 0.05), DBP index

(R=0.304 p< 0.05), W/H (R=0.533 p< 0.05 and BMI (R=0.588 p< 0.05) that was stronger than in the CT/TT group (SBP index R=0.138, pNS, DBP index R=0.292 p< 0.025, W/H R=0.554 p< 0.05 BMI R=0.186 pNS) Anova < 0.05.
Conclusions: This study exhibited higher correlation between the inflammatory marker hsCRP and DBP, SBP, BMI and W/H ratio in the CC polimorphism of p22phox, so it can be a factor that contributed to inflammation.

P1-d3-378 Fat Metabolism, Obesity 6

Non-obese girls exhibit different metabolic effects of ectopic fat based on race and ethnicity

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Background: Among obese subjects, racial/ethnic differences exist in fat deposition & its effect on insulin resistance(IR) severity. Whether such differences are present in non-obese children is unknown.
Objective and hypotheses: Assess hepatic fat fraction (HFF), visceral (VAT) & subcutaneous(SAT) abdominal adipose tissue volumes, and markers of IR in African-American(AA), Hispanic(H),& non-Hispanic(NH) White girls to test if non-obese girls' fat distribution varies by ethnicity/race and predicts IR better than BMI.
Methods: Cross-sectional study of HFF (n=57,see table),

	Number of Subjects*	Mean BMI-Z score*	Mean Waist Circumference (cm)*	Mean Age (years)*	Mean Estradiol (pg/mL)*	Mean Self-Assessed Breast Tanner Stage*
African-American (AA)	12	0.6±0.6	70.2±5.1	12.4±0.9	80.2±96.4	3.1±1.1
Hispanic (H)	16	0.5±0.8	74.5±10.7	12.4±1.0	68.0±86.9	3.2±1.1
Non-Hispanic (NH)	29	0.3±0.8	66.5±17.0	12.6±1.2	54.2±39.8	2.9±1.1

[Subject Characteristics]
**p-values were non-significant for all race/ethnicity comparisons*

and VAT/SAT at L4 (n=30; 10AA, 10H, 10NH) in non-obese girls. BMI-Z score (BMI-Z), waist circumference (WC), fasting insulin (FI) and glucose, sex hormone binding globulin (SHBG), adiponectin (ADIPO), estradiol, & HOMA-IR were obtained. 3T MRI measured HFF, VAT, & SAT.
Results: HFF correlated strongly with FI(r-0.73), HOMA-IR (r=0,73), ADIPO (r=-0.83), & SHBG (r=-0.82) in H (all p≤0.01), but not in AA & NH girls. At HFF just above the normal range (>2%), H girls had higher FI than either AA (p< 0.05) or NH (p< 0.01) girls. VAT correlated with FI & HOMA-IR only in H subjects; however, both H & AA girls had significantly higher FI & HOMA-IR than NH (all p≤0.02) when adjusted for VAT. Among all subjects, WC correlated significantly with HFF (r=0.38), SAT (r=0.86), FI (r=0.50), HOMA-IR (r=0.5), SHBG (r=-0.57), & ADIPO (r=-0.45), and in each case the correlations were stronger than those of BMI-Z.
Conclusions: Non-obese girls show metabolic effects of fat deposition that vary by race/ethnicity. Hepatic fat affects indicators of IR earlier in H non-obese girls. In non-obese AA & H girls, VAT affects IR indicators more than NH girls. In general, WC appears superior to BMI in predicting HFF & other measures of evolving IR in non-obese girls.

P1-d3-379 Fat Metabolism, Obesity 6

A proteomic approach to evaluate the role of cocoa consumption in the inflammatory pathway

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Background: Diet has been demonstrated to play a crucial role not only for the reduction of excessive energy intake but also for the normalization of tissue inflammation.Dietary components such as polyphenols present in cocoa have important health properties including modulation of immune function and inflammation. Monocytes are key to this inflammatory status and offer an important model in investigating the role of dietary components and their metabolites.
Objective and hypotheses: The main target of this research was to study the molecular mechanisms through which the bioactive components of cocoa may modulate the inflammatory state in healthy subjects.
Methods and results: At present, there is no specific report on the efficacy of bioavailable flavanols on inflammation in humans. For this reason a LC-MS analysis was performed to evaluate the bioavailability of epicatechin, in particular the glucuronide metabolite, in the plasma of four healthy volunteers treated with acute and chronic levels of cocoa. Cocoa was administered in the form of chocolate bars, derived from two batches of chocolate with different percentages of cocoa (40% and 80%).At the same time, peripheral mononuclear cells were isolated from the blood of the same subject,before and after administration.Cells were lysed and analyzed by 2D-electrophoresis with IPG strips 5-8 pH, with the respective proteomic profiles compared using PDQuest statistical software. Overall, the analysis showed an average total of 705 spots (n=4) present within the monocytes isolated. Following a deeper analysis, our attention was drawn to a cluster of spots where we observed differences in protein expression after three hours of administration of cocoa, when compared with the basal profile.
Conclusions: The data obtained from the bioavailability experiments and proteomic analyses represent the initial phase of an ongoing study that will contribute to understanding the role of diet on inflammatory mechanisms linked to cocoa consumption.

P1-d1-380 GH and IGF Physiology and Treatment 1

Autosomal dominant isolated growth hormone deficiency resulting from a recurrent *GH1* gene mutation (p.Arg183His) in three unrelated families

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Background: Isolated growth hormone deficiency (IGHD) type II results from autosomal dominant (AD) *GH1* gene molecular defects.
Objective and hypotheses: To investigate *GH1* gene mutations in patients with severe IGHD having at least one affected first degree relative.
Methods: We were able to perform biochemical and genetic studies in 7 out of 10 adults and 4 children from 3 unrelated families. IGHD was confirmed by low stimulated GH (GHmax < 3.0 ng/ml), low IGF-I levels, normal TSH response to TRH and normal levels of prolactin and cortisol. The whole *GH1* gene was PCR amplified and automatically sequenced.
Results: In adults, height SDS ranged from -5.41 to -2.28 in 6 affected and from -2.03 to -0.28 in 3 unaffected. In children, heights were -3.36, -3.28 and -2.83 in 3 affected and -0.10 in 1 unaffected subject. *GH1* gene sequencing revealed a c.626G>A transition in exon 5, predicted to result in the missense mutation p.Arg183His in every affected family member. Two other heterozygous uncommon intronic variants (c.10+52A>G, rs201477005 and c.10+56A>T, rs200389180) were also found in those subjects carrying the mutation.

Two patients who received adequate rhGH replacement therapy for 1.5 and 9.3 years showed good growth response and improved height SDS from -3.80 to -2.29 and -3.36 to -0.88, respectively.
Conclusions: As it has been previously reported for carriers of the p.Arg183His *GH1* mutation, we found a large height SDS variability among affected individuals, with adult heights ranging from -5.41 to -2.28. Due to the frequent report of this mutation, both worldwide and in our country, we would suggest to search for this variant as the first molecular study for type II IGHD.

P1-d1-381 GH and IGF Physiology and Treatment 1

Effect of growth hormone (GH) for induced seizures

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Some patients with growth hormone (GH) deficiency suffer from seizures during GH therapy. To elucidate a possible role for GH in the pathogenesis of seizures, we studied the changes in immunoreactive-somatostatin (IR-SRIF), IR-neuropeptide Y (IR-NPY), gamma-aminobutyric acid (GABA), SRIF mRNA, and NPY mRNA in the spontaneous dwarf rat (SDR) brain after treatment with rat GH (rGH) and insulin-like growth factor type I (IGF-I).
In another study, we determined the concentrations of aspartate (Asp), glutamate (Glu), and GABA in microdialysate from the SDR striatum using a microdialysis method after treatments with GH and IGF-1.
Chronic treatment with IGF-I induced significant decreases in IR-NPY in the hippocampus, as compared to the control. By contrast, chronic treatment with rGH induced a significant increase in IR-NPY in the striatum, as compared to the IGF-I treatment. The SRIF and GABA levels in acute and chronic treatments with both GH and IGF-1 did not change. Chronic treatment with rGH and IGF-I induced a significant change in NPY mRNA in the striatum and hippocampus. In addition, the concentrations of Asp, Glu, and GABA in microdialysate from striatum treated with GH and IGF-1 did not change.
Growth hormone can regulate SRIF, NPY, and GABA, although the mechanism of the action of GH in the central nervous system remains to be clarified and warrants further investigation.

P1-d1-382 GH and IGF Physiology and Treatment 1

Intracellular response to growth hormone (GH) in fibroblast cultures from normal adolescent boys

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Background: GH promotes cellular division and differentiation by activating intracellular signaling factors such as JAK2 and STAT5b. There is scarce information regarding possible differences in the total contents of JAK2 and STAT5b and in the activation of these proteins by GH in fibroblast cultures during puberty
Objective and hypotheses: To determine the total content of JAK2 and STAT5b and the effects of GH on these proteins in fibroblast cell cultures from normal male adolescents
Methods: We developed primary skin fibroblast cell cultures from 21 pubertal boys: 12 in Tanner2/3 and 9 in Tanner 4/5. We determined the total and phosphorylated contents of JAK2 and STAT5b in the cytoplasm and nucleus by Western Blot. The intracellular sensitivity to GH was determined by stimulating the fibroblast cell cultures with recombinant GH 200 ng/ml for 5, 15, 30 and 60 minutes. Results are shown in the Table as mean ± SEM, and the response to GH as area under the curve (AUC).

Results:

	Tanner 2/3	Tanner 4/5
Age (years)	11.6±0.4*	14.5±0.4
BMI (SDS)	1.28±0.35	0.72±0.34
Cyt Total JAK2/actin	2.13±0.38*	0.73±0.05
Cyt Total STAT5/actin	2.79±0.29*	0.59±0.04
Nuc Total STAT5/actin	1.01±0.11	0.95±0.23
Cyt AUC JAK2	7.6±1.4*	1.8±0.8
Cyt AUC STAT5b	62.6±16.9	100.1±25.8
Nuc AUC STAT5b	41.9±10.6	35.8±5.3

[Table 1]
* $p < 0.05$ Tanner2/3 vs Tanner 4/5

The T2/3 boys had higher fibroblast cytoplasm JAK2 and STAT 5 content, and after stimulating with GH, they showed a higher response for cytoplasm JAK2 AUC compared with T4/5 boys.
Conclusions: We conclude that boys in T2/3 have higher JAK2 and STAT 5b content and response to GH in cytoplasm compared with T4/5 boys. This finding may be related with the increased growth velocity observed during early puberty in boys.

P1-d1-383 GH and IGF Physiology and Treatment 1

50 years of the insulin tolerance test (ITT). Are we using the optimal sampling times?

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Background: GH response to insulin-induced hypoglycaemia was first reported 50 years ago. The selection of 0, 20, 30, 60, 90 and 120 minute time points - which are still used with minor variations in most protocols worldwide - was recommended to determine the near maximum GH values.
Objective and hypotheses: To review selection of GH sampling time points in order to avoid overdiagnosis of GH deficiency.
Methods: Results of 459 paediatric ITTs using the same protocol and same GH assay with time points: -30, 0, 30, 60, 90 and 120 min. A successful test was defined by a blood glucose nadir lower than 2.2 mmol/l and clinical symptoms of hypoglycaemia. GH deficiency (GHD) was defined by peak GH < 7mcg/l.
Results: Hypoglycaemia was achieved in 97% of tests. The glucose nadir occurred at 5,15,20,30 min in 1%,17%, 64%,19% of tests respectively. Peak GH was measured (in decreasing order) at 60, 30, 0, -30 , 90 and 120 min (46%, 20%, 15%, 13%, 4% and 1% respectively). GH concentrations >7mcg/l at -30 min were seen in 18 cases and represented the maximum level in 13 of them. This precluded GHD and further testing in 3% of cases (13/445). Using the same criteria, GH was precluded with the 0 min sample in 11 tests (2%), 30 min sample in 17 tests (4%), 60min sample in 21 cases (5%). The 90 and 120 min samples did not preclude GHD.
Conclusions: 90 min and 120 min GH (but not cortisol) sampling times can be omitted from ITT protocols. GH peaks that preclude GHD can be seen in samples even before the administration of insulin in 3% of tests. With 30 min sampling intervals most GH peaks are seen at 60 min after administration of insulin. GH secretion studies however demonstrate a 15-20 min half-life for GH, indicating that more frequent sampling (additional samples at 15, 45, 75min for example) would offer significant improvements in precluding GHD, reducing unecessary further tests and potentially inappropriate and costly GH treatment.

P1-d1-384 GH and IGF Physiology and Treatment 1

A novel (p.Leu213Phe) and 2 recurrent (p.E35GfsX17 and p.Asn276Ser) *IGFALS* gene mutations in two children presenting IGF-I and IGFBP-3 deficiencies

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Introduction: ALS deficiency (ALS-D) resulting from *IGFALS* gene defects has been characterized in children with severe IGF-I and IGFBP-3 deficiencies associated to mild growth retardation.
Case study: Two unrelated children were referred to the pediatric endocrinologist because of parent concern regarding their children growth. Despite having normal height, biochemical evaluation resulted in unexpected IGF-I and IGFBP-3 deficiencies. Clinical, auxological, biochemical and genetic data are shown in the table. Based on these studies, ALS-D was suspected.

	Patient 1 (girl)	Patient 2 (boy)
Birth length (cm) / birth weight (g)	49 / 2890	48 / 2710
Age / Bone age (years)	4.7 / 3.5	4.7 / 3.0
Height, cm (SDS) / weight, kg (SDS)	99.0 (-1.28) / 13.4 (-2.21)	100.0 (-1.67) / 14.2 (-2.17)
Phenotypic features	Triangular face shape, protruding forehead, discrete low nasal bridge	Triangular face shape, protruding forehead, low nasal bridge.
Adjusted target height (SDS)	-0.73	-1.41
Stimulated GH peak (ng/ml)	7.6	15.3
IGF-I (ng/ml) Reference range: 49-289	< 25	38
IGFBP-3 (µg/ml) Reference range: 1.0-4.7	< 0.5	0.8
IGFALS gene	p.E35GfsX17 (c.103dupG) / p.Asn276Ser (c.827A>G)	p.Leu213Phe (c.637C>T)

[Clinical, biochemical and genetic data]

IGFALS gene sequencing revealed that the girl was compound heterozygous for 2 already described mutations (p.E35GfsX17 and p.Asn276Ser), while the boy was homozygous for a novel missense mutation (p.Leu213Phe). This last mutation, affecting a highly conserved leucine residue, was not found in 196 controls and is predicted to be probably damaging by *in silico* analysis.
Conclusions: These two cases illustrate the broad spectrum of clinical presentation in ALS-D patients, despite the consistent finding of IGF-I and IGFBP-3 deficiencies. Interestingly, features of GH deficiency have not been previously reported in ALS-deficient patients. Usually, ALS deficiency is diagnosed later, probably because linear growth remains almost normal during the first years of life. Careful follow-up of these patients will clarify if they are able to remain growing within normal limits or if they will further deteriorate their heights.

P1-d1-385 GH and IGF Physiology and Treatment 1

IGF-I in children with non-alcoholic fatty liver disease (NAFLD)

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Background: Despite the increased incidence of NAFLD as one of the main comorbidities of obesity, a reliable biomarker to identify children with NAFLD is still lacking. Studies on adult population revealed a potential role of IGF-I as anti-inflammatory factor involved in NAFLD. Studies in pediatric population are actually lacking.
Objective and hypotheses: Our aim was to investigate the relationship between IGF-I serum levels and NAFLD in obese children.
Methods: 39 obese subjects (18F/21M), age 11.35 ± 2.31yrs were studied. Anthropometry, metabolic parameters, body composition (assessed by DEXA), IGF-I serum levels (expressed as SDS) and liver ultrasonography were assessed.
The study population was subdivided into two groups according to the presence of NAFLD diagnosed on liver ultrasonography. Differences between the groups were assessed by Mann-Whitney non-parametric U-test.
Results: 22 subjects showed NAFLD (group 1), whereas 17 subjects showed no signs of NAFLD (group 2). No significant difference between group 1 and 2 was found in BMI (3.48 ± 1.59 vs 3.07 ± 1.23 SDS). Group 1 showed significantly lower birth weight SDs (-0.37 ± 1,23 vs 0.59 ± 0.98 SDs, $p< 0.05$), birth length (49.86 ± 3.7 vs 52.3 ± 1.77 cm, $p< 0.05$), QUICKI (0.32 ± 0.035 vs 0.33 ± 0.028, $p< 0.05$) and IGF-I serum levels (-0.91 ± 0.87 vs -0.21 ± 1.032 SDS, $p< 0.05$).
Conversely group 1 showed significantly higher wc/height ratio (0.63 ± 0.59 vs 0.59 ± 0.46, $p< 0.05$), and higher insulin (24.84 ± 16.17 vs 14.97 ± 7.7 µUI/ml, $p< 0.05$), AST (38.86 ± 20.86 vs 26.12 ± 7.48 UI/L, $p< 0.05$) and ALT serum levels (42 ± 32.63 vs 24.82 ± 14.05 UI/L, $p< 0.05$). and a tendency to a higher trunkal fat mass (14695.66 ± 4545.78 vs 12181.07 ± 1952.15 g, $p=0.067$).
Conclusions: Our findings suggest that IGF-I levels could represent a biomarker to identify obese children with higher risk of NAFLD.

P1-d1-386 GH and IGF Physiology and Treatment 1

Coexistence of growth hormone and glucocorticoid resistance in cases of Laron syndrome can be the reason of poor response to IGF-1 therapy

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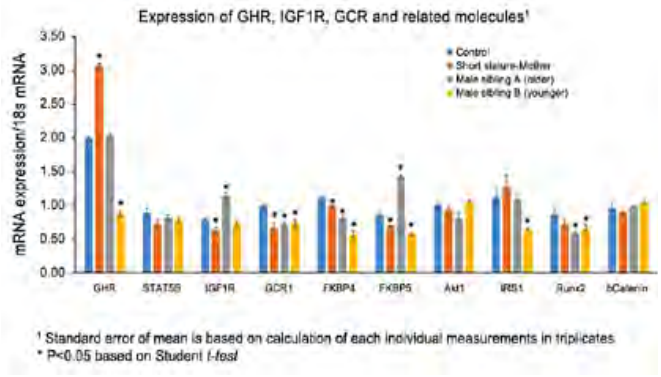
Background: Conformational changes or mutation of growth hormone (GH) receptor (GHR) frequently results to Laron syndrome leaving treatment with rIGF1 as treatment of choice. Some cases present with rIGF1 insensitivity, and this is poorly understood.
Objective: Assess expression of key signaling molecules relevant to GHR and Glucocorticoid receptor signaling in cases of rGH and rIGF1 treatment insensitivity.
Methods: Two male siblings with homozygous GHR mutation, their heterozygous mother with normal height and 5 control individuals with normal height were recruited from which mRNA was extracted. Real-time RT-PCR was performed for: GHR, STAT5b, IGF1R, IRS1, AKT1, osteoblast differentiation factor RUBx2, β-Catenin, GCRα, FKBP4 and FKBP5.
Results: Sibling A and sibling B with height SDS -4.0 and -5.7 respectively and poor response to both rGH and rIGF1. Sibling A had milder phenotype

with partial rIGF1 response and progressed to -3.0 SDS, while sibling B had no significant and had final height -5.7 SDS. The real-time RT-PCR study results are showin in table 1. Sequencing of GCRα (NR3C1) revealed SNP rs6196 T>C.

Conclusions: Poor response to rIGF1 in Laron syndrome is associated with decreased expression of IGF1R, STAT5B, RUNx2 and IRS1 molecules. Dcreased levels of GCRα and FKBP4 expression suggest glucocorticoid resistance that has to be tested in future. Detected SNP rs6196 may suggest that GCRα gene in IGF1r-resistant Laron syndrome may be more susceptible to genetic variations and change in epigenetic regulation. Potential coexistence of GH resistance and glucocorticoid resistance may explain poor growth response to IGF-1 therapy.



[Table 1]

P1-d1-387 GH and IGF Physiology and Treatment 1

Identification of two novel heterozygous molecular defects in the *IGF-1R* gene in familial short stature with intrauterine growth retardation (IUGR) and normal cognitive development

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Background: Various degrees of intrauterine, post natal growth retardation, cognitive impairment and GH treatment response have been described in *IGF-1R* mutations.

Objective and hypotheses: To analyze the *IGF-1R* gene in 10 short patients born with IUGR and normal or elevated IGF-I levels.

Results: We identified two unreported *IGF-1R* molecular defects in two patients and their affected family members. The first patient and his mother carried a heterozygous one nucleotide insertion which introduced a premature termination codon at codon 469 of the open reading frame on one allele (N417EfsX52) in *IGF-1R cDNA*.

In the second case, direct DNA sequencing revealed a heterozygous nucleotide substitution, changing a glycine to an arginine (G1152R), located in the tyrosine kinase domain and predicted to be damaging by Polyphen.

The same defect was identified in her brother and her father. Birth lengths of these individuals (patient 1, 2 and patient 2's brother) varied between -5.4 and -3.4 SDS and their birth weights from -3.8 to -2.7 SDS. They had a normal puberty. hGH treatment showed a modest efficacy for patient 1 with elevated IGF-1 serum levels and no effect for patient 2 and her brother. Despite a microcephaly (HC from -4 to -2.1 SDS), they had a normal intelligence.

Interestingly, the father of patient 2 developed diabetes mellitus at the age of 37 yrs. Final height attained with no hGH treatment was 148 cm (-2.9 SDS) for the mother of patient 1 and 150 cm (-4.2 SDS) for the father of patient 2.

Conclusions: We report two families bearing IGF-1R molecular defects predicted to result in a diminished activity of this receptor. This result supports a key role for IGF1 signaling in intrauterine and postnatal growth but demonstrates that partial IGF-1 resistance can be associated with normal cognitive function and could favor insulin resistance and diabetes. Functional studies using primary dermal fibroblasts are ongoing.

P1-d1-388 GH and IGF Physiology and Treatment 1

Optimisation of growth hormone treatment in children born small-for-gestational-age (SGA): addition of metformin raises adiponectin levels and reduces the gain of visceral fat

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Background: Short children born SGA are highly sensitive to insulin, have elevated levels of circulating high-molecular-weight (HMW) adiponectin, and partition their abdominal fat mass so that there is an elevated ratio of visceral to subcutaneous fat (JCEM 2009). Growth hormone (GH) therapy in prepubertal SGA children has normalizing effects on height, weight and lean mass but is also accompanied by insulin resistance, by low levels of HMW adiponectin and by an even more viscerotropic partitioning of abdominal fat (JCEM 2010).

Objectives: In GH-treated SGA children, we tested whether add-on therapy with metformin raises HMW adiponectinemia and reduces the gain of visceral fat..

Subjects and methods: We performed a randomized, placebo-controlled study in prepubertal SGA children (N=27; mean age 8 yr) already on GH therapy for 1-3 yr (dose 35-50 mcg/kg/d): placebo or metformin (425 mg/d) was added daily for 9 mo.

Results: Over 9 mo, the addition of metformin was accompanied by less gain of visceral fat (P=0.01) and by a higher increment of HMW adiponectinemia (P=0.008) than the addition of placebo; no significant differences were detected in growth velocity, total-body composition (by DXA), intrahepatic lipid content (by MRI) or carotid intima-media thickness (by US). The addition of placebo or metformin did not appear to be accompanied by noteworthy side effects.

Conclusion: The present results were obtained in a small study population and over a short timespan, but they provide placebo-controlled evidence that the endocrine state and the body composition of short SGA children is normalized more by GH plus metformin than by GH in monotherapy. One of the mechanisms potentially underpinning the beneficial effects of add-on metformin is LKB1-mediated, subcutaneous adipogenesis (Diabetes 2013). Larger and longer trials may disclose that a combination of GH and metformin does normalize the adult stature and body composition of SGA children more than GH does alone.

P1-d1-389 GH and IGF Physiology and Treatment 1

Three years growth response to growth hormone treatment in very young children born small for gestational age: data from KIGS

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Background: Spontaneous catch-up growth may occur by 2 years of age in approximately 85% of the children born small for gestational age (SGA). However, some SGA children with poor growth during the initial months of life will remain short during childhood and as adults.

Objective and hypotheses: To evaluate the 3 year growth response to GH treatment in very young short children born SGA, and to test in these age group the existing predictions models for growth response developed for SGA children with older ages.

Methods: KIGS (The Pfizer International Growth Database) was queried for children on GH treatment with birth length and/or weight below -2SDS with age at start of therapy older than 2 and less than 4 years and between 4 and 6 years.

Results: A total of 156 SGA patients (100 boys) were selected in the 2-4 yrs group (median age 3.3 years, height SDS -3.9, weight SDS -3.8) and 464 SGA children (284 boys) in the 4-6 yrs group (median age 4.9 years, height SDS -3.4, weight SDS -3.1). Height velocity was below the mean for both groups. The two SGA groups presented a significant increase in height velocity. As a result, median height SDS increased from -3.9 at start of GH therapy to -2.2 SDS at 3 yrs in the 2-4 yrs group and from -3.4 to -2.0 SDS in the 4-6 yrs group. Median weight SDS increased from -3.8 to -2.1 SDS in the 2-4 yrs group. Respective values for the 4-6 yrs group were -3.1 to -1.6 SDS. The observed height velocity for the first and second years could be estimate by the SGA model.
Conclusions: In this observational database, very young children born SGA without spontaneous catch-up growth presented a significant improvement in height and weight gain during the three years of GH treatment, comparable to the older age group. The prediction model developed for older SGA children can be applied in the very young cohort as well.

P1-d1-390 GH and IGF Physiology and Treatment 1

Four years of safety and efficacy of a once-weekly formulation of rhGH (LB03002) in children with GHD

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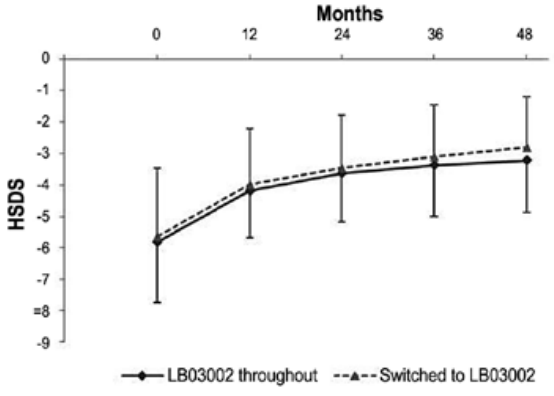
Background: We have previously shown that the growth response with once-weekly LB03002 in children with GHD is comparable to that with daily GH, demonstrating clinical comparability within 12 months of treatment and achieving expected growth rates for 24 months.
Objective and hypotheses: This study was extended in two countries for an additional two years to assess the long-term safety and efficacy of LB03002.
Methods: 67 previously untreated children with severe growth retardation due to GH deficiency (GH peak ≤ 7 ng/mL in two tests) received either once weekly 0.5 mg/kg LB03002 (LB03002 throughout) or once daily 0.03 mg/kg rhGH (Switched to LB03002) for 12 months. Patients treated with daily rhGH were then switched to LB03002 and all patients continued treatment with once-weekly LB03002 for another 36 months.
Results: The development of linear growth assessed by height (H), HSDS, height velocity (HV) and HVSDS showed excellent response to once-weekly LB03002 throughout the 4 year treatment period, comparable for both treatment groups. Long-term growth response was in line with published studies on daily rhGH.



[Mean HSDS (± SD) during rhGH treatment]

IGF-I levels increased towards the normal range without abnormal elevation of the IGF-I/IGFBP-3 ratio. The BA/CA ratio increased throughout treatment, demonstrating expected but not premature skeletal maturation. A mean HV of approximately 6 cm/year at month 48 showed the potential for further growth. LB03002 was well tolerated with most AEs being mild and unrelated to treatment.
Conclusions: Safety and efficacy of weekly treatment with LB03002 over 4 years has been demonstrated, making once-weekly LB03002 a viable candidate for the treatment of GH-deficient children.

P1-d1-391 GH and IGF Physiology and Treatment 1

Pre-clinical characterization of MOD-4023, a long acting growth hormone supporting phase II in GHD pediatric population

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Background: Prolor Biotech develops long acting human GH utilizing CTP technology. The technology involves fusion of the C terminus peptide of β-hCG to the target protein. CTP enabled the production of a long-acting hGH (MOD-4023), obviating the need for the numerous daily injections supporting single weekly injection in growth hormone deficient patients.
Aims: To characterize MOD-4023 non-clinical toxicology, supporting clinical studies in pediatric population.
Methods: The pharmacological effects of MOD-4023 have been examined in vivo in hypophysectomized rats. In addition, MOD-4023 pharmacokinetics and pharmacodynamics profiles have been extensively evaluated in rats and in Rhesus monkeys and compared to a daily hGH regimen, followed by safety evaluation in those animals.
Results: MOD-4023 potency was assessed in vivo. Weight gain, a primary pharmacodynamic effect of GH, was determined in hypophysectomized rats. The accumulated weight following 4 days of daily injection of r-hGH was equivalent to that observed following a single injection of MOD-4023. The results of nonclinical pharmacokinetic studies conducted in rats and immature rhesus monkeys consistently demonstrated a dose-proportional exposure and response as reflected by IGF-1. In both rats and immature monkeys repeated dose and reproductive and developmental toxicity studies, the NOAEL was the highest MOD-4023 administered dose.
Conclusion: MOD-4023 demonstrated an excellent safety profile in all relevant pre- clinical models. Combined with a significant prolonged GH activity compared to the current marketed daily hGH. MOD-4023 has the potential to replace the frequent (daily) injections now required for the treatment of GHD with a weekly regimen in children. It is anticipated that the doses administered to pediatric patients would be several orders of magnitude below the exposures obtained in these studies and thus would not represent a safety issue in this population.

P1-d2-392 GH and IGF Physiology and Treatment 2

Improvements in cognitive function following GH treatment: is there a catch-up effect?

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Background: A cognitive effect of GH treatment has been proposed.
Objective and hypotheses:
1) to study if a relationship can be identified between GH deficiency and cognitive functioning (IQ scores) prior to GH treatment.
2) to identify if within group changes have occurred following 24 months of GH treatment.
Methods: Participants were short (-2 SDS), pre-pubertal (3-11 years of age at start) who completed IQ testing at baseline and 24 months of GH treatment. A multicenter, longitudinal, non-blinded, parallel-group study conducted in Sweden (4 sites) with imbalanced randomisation [2:1] individualized (17-100ug/kg/d) or fixed (43ug/kg/d). Outcomes examined were full IQ (FIQ), verbal IQ (VIQ), and performance IQ (PIQ) measured using WPPSI and WISCIII test packages.

Results: 94 participants grouped into ISS (n=56) & GHD (n=38) according to GHmax AITT/24h of 10ug/L. Baseline mean IQ for the whole population was 94 FIQ points. At 24 months the mean FIQ score increased to 102 points ($p< 0.005$). PIQ increased ($p< 0.001$) but VIQ was unchanged. At 24 months increases in FIQ scores were found for the whole population ($p< 0.005$) & PIQ ($p< 0.001$). No change in VIQ was found. A within group analysis showed that the GHD group made significant improvements in FIQ ($p< 0.001$), PIQ ($p< 0.001$) and VIQ ($p< 0.033$). The ISS group improved in PIQ only ($p< 0.004$). Between group differences were found at baseline in FIQ (GHD: 96; ISS: 103; $p< 0.17$) and PIQ (GHD: 95; ISS: 103; $p< 0.011$). At 24 months the FIQ score differences between the groups were no longer significantly different.
Conclusion: IQ score differences were found between GHD and ISS children prior to GH treatment. IQ scores improved for the whole group during the 24 month study period. Children with GHD improved in more areas than ISS children. Our data indicates that GH status is related to IQ scores. The data also lends support for the routine assessment of cognitive functioning in GH treated children.

P1-d2-393 GH and IGF Physiology and Treatment 2

Aromatase inhibitor treatment in peri-pubertal males with growth disorders augments height while maintaining bone age/chronological age ratio

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Background: The American Norditropin Studies: Web-enabled Research (ANSWER) Program®, a US-based registry, has collected data on patients treated with Norditropin® (somatropin rDNA origin, Novo Nordisk A/S).
Objective and hypotheses: To analyze baseline characteristics and longitudinal data in growth hormone (GH)-treated patients who were prescribed aromatase inhibitor therapy (AIT: anastrozole or letrozole) at the discretion of their physicians.
Methods: As of September 2012, 57 male GH-naive patients with GH deficiency (GHD, n=34), idiopathic short stature (ISS, n=17), or other growth disorders (n=6) were included in this analysis.
Results: For the overall population (n=57), mean (±SD) chronologic age (CA) at GH and AIT start were 12.2±3.3 yrs and 15.1±1.9 yrs, respectively. Mean height standard deviation score (HSDS) increased from baseline (-2.1 ±0.8) to start of AIT (-1.1±0.8). In a longitudinal population of 13 patients (6 GHD, 6 ISS and 1 other), the mean duration of GH treatment (GHT) before AIT was 3.8±2.6 yrs and mean duration of AIT was 1.3±0.4 yrs. HSDS increased steadily from baseline through AIT. Bone age (BA) also increased from baseline through AIT, but mean BA/CA ratio remained stable for more than one year after AIT initiation.

	Baseline		Start of AIT		During or After AIT (2011)*		After AIT (2012)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Age	13	10.2 (4.2)	13	14.0 (2.1)	13	14.9 (2.2)	13	15.3 (2.1)
HSDS	13	-2.29 (0.44)	13	-1.17 (0.64)	13	-0.83 (0.65)	13	-0.70 (0.63)
BA	9	9.4 (3.9)	13	13.1 (0.9)	13	14.1 (1.5)	13	14.6 (1.3)
BA/CA	9	0.81 (0.17)	13	0.96 (0.14)	13	0.96 (0.13)	13	0.96 (0.12)

[Figure 1: Patient characteristics before, during and after AIT]
* Five of the 13 longitudinal patients ceased AIT prior to the end 2011 analysis period

A positive correlation was observed between the duration from AIT initiation and change in HSDS ($R=0.52$, $p< 0.05$).
Conclusions: In this longitudinal population, a continued increase in HSDS occurred concurrently with a stable BA/CA ratio for more than one year after AIT initiation, which is consistent with a potential effect of AIT in slowing bone maturation and prolonging the period during which GHT may increase growth.

P1-d2-394 GH and IGF Physiology and Treatment 2

Recombinant human insulin-like growth factor-1 (IGF-I) therapy in Duchenne muscular dystrophy (DMD)

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Background: DMD is an X-linked progressive muscle disorder treated with glucocorticoids (GC), which delay motor decline, but cause significant endocrine adverse effects. IGF-I offers potential as a therapeutic agent: it may improve or preserve muscle function, and counter GC effects of growth failure and insulin resistance.
Objective and hypotheses: To determine if IGF-I therapy 1) improves linear growth and 2) improves or preserves muscle function in DMD. We hypothesized that IGF-I therapy would improve growth and muscle function in GC-treated DMD boys compared to controls.
Methods: Prospective randomized controlled trial of IGF-I therapy in prepubertal, ambulatory, GC-treated DMD boys (n=17) compared to controls (GC alone, n=21). IGF-I 160 mcg/kg was given daily subcutaneously for 6 months. Primary endocrine outcomes were height velocity and change in height SD score (ΔHtSDS). Other outcomes included changes in timed motor tests, cardiopulmonary function, insulin sensitivity and safety.
Results: Height velocity in IGF-I treated subjects was double that of controls at 6 months (6.5 ± 0.4 vs. 3.3 ± 0.3 cm/yr, $p< 0.0001$). HtSDS increased in treated subjects over 6 months, while declining in controls ($+0.12 \pm 0.03$ vs. -0.13 ± 0.02, both $p\leq 0.001$). The annualized difference in ΔHtSDS was 0.50 ± 0.14 in treated over control subjects ($p< 0.0001$). There were no significant differences between groups for changes in neuromuscular and cardiopulmonary outcomes. Fasting glucose remained normal, but fasting insulin and HOMA-IR decreased (by 4.4 ± 2.0 mU/L and 0.9 ± 0.4 units respectively, both $p< 0.05$) in treated vs. control subjects. Significant treatment-related adverse events were transient intracranial hypertension (n=1) and asymptomatic papilledema (n=1).
Conclusions: In this first study of IGF-I therapy in DMD boys, 6 months of once-daily IGF-I significantly increased height velocity and HtSDS compared to controls, but there was no difference in motor functional outcomes.

P1-d2-395 GH and IGF Physiology and Treatment 2

Efficacy of rhGH/rhIGF-1 co-administration therapy in children with short stature, low IGF-1 and GH sufficiency: results from a phase II, randomized, open-label, active-controlled trial

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Background: Growth disorders due to defects in the GH-IGF-1 axis form a continuum from growth hormone (GH) deficiency to GH resistance, with varying responsiveness to rhGH therapy. Children with short stature, low IGF-1 concentrations and GH sufficiency may require high doses of rhGH to reach IGF-1 titration targets. In these children, rhGH/rhIGF-1 co-administration (co-admin) may be advantageous over mono-therapy with rhGH alone to promote linear growth.

Objectives and hypothesis: Assess efficacy and safety of rhGH/rhIGF-1 co-admin vs rhGH alone in treatment-naïve, prepubertal children (baseline height SDS ≤−2, IGF-1 SDS ≤−1 and maximum stimulated GH ≥10ng/mL).
Methods: In this open-label trial, 106 patients were randomized to receive either rhGH only or one of three co-admin regimens (rhGH 45µg/kg QD plus separate injections of 50, 100 or 150µg/kg rhIGF-1 QD). The primary analysis was ANCOVA (dependent variable: Year 1 height velocity [HV]; covariates: baseline age and IGF-1 SDS) using the modified intention-to-treat (mITT) population.
Results: Baseline overall age was 8.8±2.1 years (mean±SD). With increasing rhIGF-1 doses there was a trend towards greater HV with co-admin vs rhGH alone, reaching significance for the 45/150µg/kg co-admin group at Year 1 (mITT and completer populations) and Year 2 (completer only). No unexpected treatment emergent adverse events (TEAEs) were reported.

	Mean±SD height velocity (cm/year, mITT* population)				Mean±SD height velocity (cm/year, completer population)			
	rhGH (n=25)	rhGH/ rhIGF-1 50µg/kg (n=27)	rhGH/ rhIGF-1 100µg/kg (n=27)	rhGH/ rhIGF-1 150µg/kg (n=26)	rhGH (n=25)	rhGH/ rhIGF-1 50µg/kg (n=27)	rhGH/ rhIGF-1 100µg/kg (n=27)	rhGH/ rhIGF-1 150µg/kg (n=26)
Year 1	9.3±1.7 (n=25)	10.1±1.3 (n=27)	9.7±2.5 (n=27)	11.2±2.1† (n=26)	9.3±1.7 (n=24)	10.1±1.4 (n=25)	10.4±1.9 (n=22)	11.4±1.9† (n=25)
Year 2	7.5±1.3 (n=24)	8.1±1.6 (n=24)	8.4±1.9 (n=22)	8.7±2.1 (n=24)	7.5±1.3 (n=22)	8.4±1.5 (n=21)	8.7±1.7 (n=20)	9.0±1.9† (n=22)
Year 3	7.3±1.9 (n=22)	6.8±1.4 (n=21)	7.6±1.8 (n=20)	6.9±1.7 (n=22)	7.3±1.9 (n=21)	7.1±1.2 (n=19)	7.7±1.8 (n=19)	6.9±1.8 (n=20)

[Mean±SD height velocity]
*with imputation for those not completing Years 1/2/3
†P< 0.05 vs rhGH alone, Dunnett's adjustment.

Conclusion: rhGH/rhIGF-1 (45/150µg/kg) co-administration resulted in significantly greater height velocity at Year 1 and 2 than rhGH alone, producing an overall greater gain in height at year 3, and without any evidence of an increase in TEAEs.

P1-d2-396 GH and IGF Physiology and Treatment 2

Factors influencing the final adult height of girls with Turner syndrome treated with recombinant human growth hormone and stanazolol

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Objective: To investigate the final adult height (FAH) of girls with Turner syndrome (TS) treated with the recombinant human growth hormone (rhGH) and stanazolol, and to analyze its influencing factors.
Methods: Sixty-four TS girls participated in the study. Thirty-eight girls (treatment group) received daily subcutaneous injection of rhGH(1.0-1.1 IU/kg.w) and oral stanozolol(0.02-0.04mg/kg.d) treatment for (2.7±1.3) years, their chronological age before treatment(CA_0) was (12.9±2.7)years, and bone age before treatment(BA_0) was (10.6±1.9)years. The other 26 girls (control group) did not receive any treatment for growth. The factors influencing the FAH of the treatment group were analyzed.
Results: FAH of the treatment group was significantly higher than that of the control group [(149.0±6.2) vs.(136.7±5.0)cm, *P*< 0.001]. The mean height gain which defined as the FAH minus the predicts adult height before treatment was (8.1±4.9)cm. According to the age at which the treatment was started, subjects were divided into five subgroups: 6.0-7.9yr, 10.0-11.9yr, 12.0-13.9yr, 14.0-15.9yr and 16.0-18.4yr groups, each group received average 4.8, 3.6, 2.6, 2.1 and 1years treatment duration respectively, and the mean height gain for each group was 14.3, 8.8, 8.5, 6.4 and 3.9 respectively. FAH was positively correlated with height SDS by reference of healthy Chinese girls at the initiation of therapy (Ht_0SDS), growth velocity at the first year treatment (GV_1), duration of treatment and genetic target height SDS, and was negatively correlated with CA_0. The height gain was positively correlated with duration of therapy and GV_1, and was negatively correlated with CA_0 and BA_0.
Conclusion: Combined rhGH and stanazolol treatment can effectively improve FAH of TS girls. TS girls with CA_0 less than 16 and BA_0 less than 12.5 may obtain satisfied FAH in 2 years duration of rhGH and stanazolol treatment. Early diagnosis and early treatment benefit the TS girls in the FAH.

P1-d2-397 GH and IGF Physiology and Treatment 2

Is there a dose-dependent effect of long-term growth hormone (GH) treatment on insulin sensitivity and β-cell function in pubertal short children born small for gestational age (SGA)?

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Background: GH treatment is effective in improving adult height (AH) in short children born SGA. Metabolic effects of GH treatment include the development of reduced insulin sensitivity. There are no data on the long-term effects of treatment with 2 doses of GH on insulin sensitivity and β-cell function in pubertal short SGA children.
Objective: To determine insulin sensitivity and β-cell function in short SGA children randomized to either 1 or 2 mg GH/m^2/d (~ 0.035 or 0.067 mg/kg/d).
Population and methods: Sixty-seven children were randomized to 1 (group 1, n=30) or 2 (group 2, n=37) mg GH/m^2/day and treated until adult height. Frequently sampled intravenous glucose tolerance were performed at adult height. Insulin sensitivity (Si), glucose effectiveness (Sg), acute insulin response (AIR) and disposition index (DI) were calculated using Bergman's MINMOD MILLENIUM software.
Results: Group 1 and 2 had similar baseline characteristics. AH was reached after median (IQR) 5.6 (5.1 to 6.5) years of GH treatment. At AH median fasting glucose levels were 4.9 mmol/L and insulin levels were 13.0 mU/L, in both groups. There was no difference in fasting insulin (P=0.47) and fasting glucose levels (P=0.18) between both groups. At AH median Si was similar in group 1 (4.52 x 10^{-4}/min^{-1} µU/ml) and group 2 (4.46 x 10^{-4}/min^{-1} µU/ml) (P=0.76). There was no significant difference in Sg (P=0.92) and AIR (P=0.83) between both groups. Beta cell function, estimated by DI levels, was also similar in the two groups, 3339.45 vs. 2811.4 (P=0.45).
Conclusion: Long-term GH treatment in two different dosages, 1 vs. 2 mg GH/m^2/d, until adult height does not result in a difference in insulin sensitivity and β-cell in pubertal short children born SGA.

Characteristics	Group 1; 1mg/m2/day	Group 2; 2mg/m2/day	P-value
Gestational age (weeks)	38 (36.5 to 39.5)	38 (36.0 to 40.0)	0.810
Birth weight SDS	-2.13 (-2.53 to -1.40)	-1.67 (-2.40 to -1.25)	0.216
Birth length SDS	-2.61 (-3.35 to -1.98)	-2.21 (-2.56 to -1.68)	0.086
Age at start of GH treatment (years)	11.65 (10.25 to 12.65)	11.2 (10.10 to 12.90)	0.59
Height SDS at start of GH treatment	-3.03 (-3.50 to -2.68)	-2.73 (-3.22 to -2.39)	0.072
Age at adult height (years)	17.20 (16.16 to 18.17)	17.47 (16.51 to 18.20)	0.724
Duration of GH treatment (years)	5.51 (5.03 to 6.04)	5.88 (5.07 to 6.69)	0.402
Adult height SDS	-2.10 (-2.63 to -1.51)	-1.34 (-2.10 to -0.94)	0.007
TH corrected adult height SDS	-1.15 (-1.76 to -0.96)	-0.65 (-1.31 to -0.21)	0.007

[Table 1. Clinical Characteristics]

P1-d2-398 GH and IGF Physiology and Treatment 2

Effects of varying growth hormone (GH) dose regimens on glucose metabolism in children born small for gestational age (SGA)

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Background: In SGA children, titration of GH dose by IGF-I levels could be a strategy for achieving the optimal balance between growth response and potential metabolic adverse effects.
Objective and hypotheses: To explore the effects of 3 different GH dose regimens on glucose metabolism in SGA children.
Method: In NESGAS clinical trial, 88 (62 boys) pre-pubertal SGA children (age±SE, 6.15±0.18yrs) received high dose GH (67 µg/kg) for 1 year to identify poor responders. Subsequently, they were randomised to one of the 3 treatment groups; 35µg/kg(Low), 67µg/kg(High), or titrated by IGF-I levels to 0 -+2 SDS(Titrated) for 2 years. They underwent a short intravenous glucose tolerance test(IVGTT) at randomisation (yr 1) and at the end of 2 years of treatment (yr 3). The insulin secretion was assessed from acute insulin response from IVGTT, and HOMA provided a measure of insulin sensitivity(IS).
Results: The baseline characteristics of age, height SDS, and fasting insulin and glucose levels at randomisation were similar in the 3 groups. After 2 years of treatment, the 'Titrated' group had the lowest increases in fasting insulin (p trends=0.003) and C-peptide (p=0.005) levels and the highest increases in IS (p=0.007).

Means (SE) n	IGF-I Titrated n=36	35mcg/kg n=23	65mcg/kg n=29	
Changes (Yr 1-3) in fasting Insulin (%)	-0.30 (8.39)	31.65 (13.87)	61.12 (22.13)	0.003
Changes (Yr 1-3) in fasting C-peptide (%)	-2.45 (6.48)	21.31 (13.72)	43.70 (18.12)	0.005
Changes (Yr 1-3) in IS (%)	21.96 (9.57)	-2.64 (7.90)	-10.26 (8.84)	0.007
Changes (Yr 1-3) in Insulin Secretion (%)	-4.04 (7.49)	12.80 (9.62)	70.34 (39.88)	0.002

[Table]

The 'High' group had the greatest increases in insulin secretion (p=0.002). However, changes in insulin secretion adjusted for IS and fasting glucose were similar in the 3 groups.
Conclusions: Favourable changes in IS associated with IGF-I titrated GH treatment is encouraging in SGA children, who are at an higher risk for metabolic decompensation. Further analysis to explore the associations of these metabolic changes with growth and IGF-I responses are important to establish the utility of this mode of treatment.

P1-d2-399 GH and IGF Physiology and Treatment 2

The effect of prolonged GH treatment on upper airways and sleep-disordered breathing of 50 non-severely obese children with Prader-Willi syndrome

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Background: Although GH therapy is suitable for Prader-Willi syndrome (PWS), some deaths, caused by respiratory insufficiency, were reported in the first months of GH treatment in these patients.
Objective and hypotheses: To establish wether long-term GH treatment in PWS could cause upper airways narrowing and sleep-disordered breathing.
Methods: Fifty non-obese children (27 boys), aged {median (IQR)} 1.9 (2.2) yrs with PWS were studied before and after 6-weeks, 6 and 12 months of GH treatment (.010-.030 mg/kg/day) and yearly thereafter. All patients underwent anthropometry, one-night 12 channels polysomnography (PSG) and ENT examination wiht flexible nasopharyngoscope. The PSG parameters considered were respiratory disturbance index (RDI), obstructive apnea index (OAI) and central apnea index (CAI). Patients with OAI >1.3 at the first evaluation were excluded from the study. Tonsils and adenoids hypertrophy were scored according Brodsky and Wang criteria. Non-parametric tests were used for statistics.
Results: The PSG finding reported in table below show an increase of OAI in the first three years and a contemporary improvement of CAI and RDI over the time. Three patients had to temporarily discontinue the GH treatment (from 2 to 4 months). ENT evaluation revealed a significant increase of adenoids ($p < .01$) and tonsils ($p < .05$) after 24 and 36 months of GH treatment. We found a correlation between OAI and adenoid hypertrophy ($p < .01$). Three patients required adenotonsillectomy.

Time (months)	0	1.5	6	12	24	36	48	p
n	50	50	37	48	22	12	8	
OAI	0.1(0.5)	0.4(0.9)	0.3(0.6)	0.5(0.9)	0.5(1.2)	0.7(0.8)	0.6(1.3)	<0.02
CAI	1.2(2.7)	0.6(1.9)	0.2(1.7)	0.1(0.9)	0.0(0.3)	0.0(0.0)	0.0(0.2)	<0.0001
RDI	1.4(2.4)	1.5(2.2)	0.7(1.9)	0.8(1.2)	0.6(1.3)	0.7(0.8)	0.8(1.4)	<0.05

[Polysomnographic findings]

Conclusions: Our findings confirm the favorable effect of long-term GH treatment on respiratory function of PWS, however the increase of OAI and upper airways narrowing reccommend ENT and PSG follow-up.

P1-d2-400 GH and IGF Physiology and Treatment 2

Population PK model of insulin-like growth factor (IGF-1) after single and repeat administration of recombinant human IGF-1 (rh-IGF1) in subjects with IGF deficiency (IGFD)

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Background: IGF-1 levels after treatment with rh-IGF-1 are more variable than those after GH treatment.
Objective: To avoid either prolonged exposure to very high or low IGF-1 levels, we developed a population PK model which describes IGF-1 serum concentrations after single and repeat subcutaneous (sc) doses of rhIGF-1.
Methods: 1873 samples from 212 prepubertal subjects with IGFD (height< -2 SD), normal GH secretion and low IGF-1 levels were obtained at prespecified times after rh-IGF-1 administration. Different structural models describing the relationship between rhIGF-1 and GH inhibition and residual error models were evaluated. Influence of covariates on PK parameters was explored and variability terms tested on various parameters. The analysis was conducted using a population approach with NONMEM software v6.2. The model was externally validated using Visual Predictive Checks.
Results: The IGF-1 time course after sc administration was well described by a one-compartment model with first order absorption and elimination incorporating a zero order input rate to characterize the endogenous formation rate of IGF-1. The absorption constant, clearance and volume of distribution were 0.789 h^{-1}, 0.753 L/h and 5.68 L respectively. Mean formation rate of IGF-1 was 64 µg/h. 5 covariates were found significant on parameters: IGF-1 baseline levels, IGFBP-3, age, weight and rh-IGF-1 dose. Interindividual variability was low on clearance and volume (~15%) and moderate for absorption rate constant (41%). The model adequately described the external dataset revealing its robustness and general applicability for prediction of IGF-1 concentrations.
Conclusions: This model allows the prediction of IGF-1 exposure after single and multiple doses, taking account of baseline IGF-1 and IGFBP-3 levels, age and weight. It could be a useful tool to optimize doses and dose regimen, titration and to estimate rhIGF-1exposure at steady state in IGFD patients from childhood to young adulthood.

P1-d2-401 GH and IGF Physiology and Treatment 2

Pubertal height gain and adult height in pre- and pubertal short SGA patients treated with GH

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Background: The available information on the efficacy of GH treatment in short SGA children starting their treatment in adolescence is limited.
Objective and hypotheses: We therefore compared the pubertal height gain (PHG) and near adult height (AH) of GH treated SGA children between those who started before the onset of puberty and those who started at onset of puberty.
Methods: From the Belgian Growth Registry, near AH (HV < 2 cm/year) was available in 96 (63 %) of 153 SGA (birth weight and/or length < -2SD) patients in whom GH was started before testis volume 10 ml or breast stage B3. In total 51 (20 boys) started at least 1 year before the onset of puberty (PreP group) (median duration 6.6 yrs, median dose 50 µg/kg.day) and 45 (20 boys) from the onset of puberty (P group) (for 4.0 yrs, dose 41 µg/kg.day). PHG (cm) was calculated as AH (cm) minus height at start puberty (cm).
Results: PHG was significantly (p< 0.005) higher in the girls of the P group (19.9 [18.1,25.7]) (median [IQR]) compared to the PreP group (18.0 [13.9,20.8] cm) and comparable for the boys (27.0 [24.2,30.4] vs 25.8 [23.7,31.4]. While in the P group a height gain of 0.5 SD was observed during puberty, no further improvement in height SDS was found in the PreP group. Median age at onset of puberty was similar and negatively correlated to PHG in boys and girls of both groups. The increase in height SDS from onset of GH therapy until AH was higher in preP group (1.0 [0.3,1.6]) than in the P group (0.6 [0.3,1.3]) (p=0.05). AH SDS was comparable in the 2 groups (-2.3 [-2.9,-1.8] and -2.7 [-3.1,-2.0]). Only 35% in the PreP and 27% in the P group achieved a AH >-2SD.
Conclusions: Even with a higher PHG in girls but not in boys, only a limited improvement in AH could be obtained in SGA children treated at onset of puberty compared to GH treated patients starting at least 1 year before puberty. Efforts should be made for earlier referral for GH treatment in case of a positive cost-effectiveness analysis.

P1-d2-402 GH and IGF Physiology and Treatment 2

Most subjects with non-severe GH deficiency do not require GH treatment until final height

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Background: A previous investigation by our group (Zucchini et al. JCEM 2006) demonstrated that 35% of the subjects with non-severe GHD show a normal secretion when retested at puberty, with a higher percentage if retesting was performed at mid puberty.
Objective and hypotheses: To confirm that GH secretion normalizes before final Ht in subjects with non-severe GHD and that GH therapy can be safely suspended, we retested a selected group of 20 subjects (15 M, 5 F; age 10.7±3.3 yrs, Ht SDS -2.37±0.4; 12 prepubertal and 8 pubescent; bone age (BA) delay 2.0±1.6 yrs; target Ht SDS -0.93±0.8) classified as non-severe GHD.
Methods: Inclusion criteria were short stature and/or pathological Ht velocity (national criteria), non-severe GHD (peaks 5-10 ng/ml), normal MRI. All cases had insulin or GHRH-arginine test after 1 month without therapy in males at Tanner stage 3-4 and in females at Tanner stage 2-3. Therapy was withdrawn in case of normal secretion. GH dose was 0.20 mg/kg/w and mean therapy duration was 4.2±1.9 yrs.
Results: 18 subjects (90%) showed a normal GH secretion at retesting (mean age 14.9 yrs). In the whole group at retesting compared to diagnosis Ht was -1.1±0.7 SDS (Ht gain 1.3±0.8 SDS; p=0.0001), IGF-1 levels 0.4±1.1 SDS vs -1.0±1.3 (p=0.001), BA delay 0.3±1.8 yrs vs -2.0±1.6 (p=0.005). IGF-1 levels at retesting were > 0 SDS in 13/18 cases vs 3/18 at diagnosis. In the 18 subjects who suspended therapy final Ht SDS was -1.26±0.8 (p=0.049 vs Ht SDS at retesting and non significant vs target Ht SDS).
Conclusions: Most of our subjects diagnosed as non-severe GHD at a mean age of 10.7 yrs showed a normal secretion and IGF-1 levels when retested at midpuberty, reaching a final ht consistent with target Ht after therapy withdrawal. The Ht gain between diagnosis and retesting was associated with a significant BA advancement. The accuracy of the initial diagnosis and the real effectiveness of treatment in these subjects should be more clearly demonstrated.

P1-d2-403 GH and IGF Physiology and Treatment 2

The association between growth hormone response and baseline body composition of children with growth hormone deficiency

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Aim: Here, the association between response to recombinant human Growth Hormone (rhGH) treatment and body composition was investigated in children with growth hormone deficiency (GHD).
Methods: Forty-two patients (21 boys and 21 girls) aged between 5.7-15.5 years (mean age: 10.8±2.6 years) with isolated GHD, who started treatment with rhGH were enrolled in this study. The auxological and laboratory data, results of bioelectrical impedance analyses were evaluated. Children with GHD were followed-up for 12 months, and according to growth response (change of > 0.7 SDS in height over one year), patients were divided into two groups as good responders and poor responders.
Results: Forty-eight percent of patients showed a good response to rhGH therapy. At study entry, mean age, height SDS, weight SDS, serum IGF-1 SDS, IGFBP-3 SDS, growth velocity prior to rhGH therapy, GH after clonidine and L-dopa were similar in the two groups. At baseline, BMI SDS and waist-hip ratio were significantly higher in good responders ($p = 0.02$ and $p = 0.006$, respectively). Good responders had higher percentages of body fat mass (FM) (26.7±8.9 vs. 16.9±5.9), lower percentages of fat free mass (FFM) (17.3±2.5 vs. 20.0±1.7) and total body water (TBW) (56.5±5.3 vs. 63.1±4.4), compared to poor responders ($p < 0.05$). There were significant correlations between changes in height SDS over one year and baseline body composition in children with GHD on rhGH treatment ($r = 0.617$ for percentage of FM, $r = -0.558$ for percentage of FFM, $r = -0.629$ for percentage of TBW, $p < 0.001$).
Conclusion: Baseline body composition data of children with GHD can be useful parameters in the prediction of growth response to rhGH treatment. Thus, estimation of rhGH dose-based FFM of the body in order to obtain a continuing height gain during treatment with rhGH is considered to be an issue that should be investigated.

P1-d3-404 GH and IGF Physiology and Treatment 3

A preliminary report: from the database on growth hormone (GH) treatment in Japanese, NordiPAD - GH effect on lipid metabolism

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Background: GH treatment is effective on growth, glucose metabolism and lipid metabolism.
Methods: We studied the effect of lipid metabolism of GH treatment on Japanese GHD children using the data of NordiPAD.
Results: 11.4 % of boys and 8.8% of girls of GHD patients had serum TC levels more than 200mg/dL. This frequency is higher than the data of normal Japanese children. 3 years after GH treatment a mean value of TC in boys was significantly decreased from 178mg/dL to 169 mg/dL. That in girls was also decreased from 183mg/dL to 175mg/dL, but this decrease was not statistically significant. In addition, a mean value of non-HDL cholesterol (non-HDL-C) in boys was significantly reduced from 114mg/dL to 106mg/dL 3 years after GH treatment. In girls with GHD, non-HDL-C was reduced from 121mg/dL to 111mg/dL. Obesity index both in boys and girls with GHD did not change during this period.
Furthermore, we analyzed changes of serum TC and non-HDL-C in patients whose serum TC levels were more than 200 mg/dl at the start of GH treatment. As results, TC was decreased from 221mg/dL to 195mg/dL in boys and from 221mg to 196mg/dL in girls 2 years after GH treatment. Non-HDL-C was also reduced from 155mg/dL to 137mg/dL in boys and from 164mg/dL to 143mg/dL in girls. All these decreases were statistically significant.
Conclusions: NordiPAD data indicates that GH treatment has impact on lipid metabolism in Japanese children with GHD. Data analysis of NordiPAD is useful for GH efficacy.

P1-d3-405 GH and IGF Physiology and Treatment 3

Relationship between either total anti-IGF-1 antibodies (ADA) or specific anti-IGF-1 IgE titres and the occurrence of apparent hypersensitivity reactions in a paediatric population treated with rhIGF-1 (Increlex®)

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Background: Increlex (mecasermin) is a human insulin-like growth factor-1 (rhIGF-1) produced by recombinant DNA technology and has marketing authorisation for the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor-1 deficiency (Primary IGFD). In three recent clinical studies, 56 cases of hypersensitivity related side effects (HRSE) were reported in 289 treated patients. These include: localized injection site reactions injection site erythema / reactions) as well as rash and urticaria.
Objective and hypotheses: The objective of the study was to assess whether or not the occurrence of these reactions could be correlated with either the presence of antibody to Increlex or with higher titres of anti-IGF-1 IgE.
Methods: A reliable method (ImmunoCAP / Phadia®) was validated for the measurement of anti-IGF-1 IgE antibodies with a detection limit of 0.1 kIU/L (0.242 ng/mL). The rationale of the study was to determine anti-IGF-1 IgE antibody titres in serum samples obtained from 182 ADA positive Increlex-treated patients, whether or not they experienced HRSE.
Results: Specific anti-IGF-1 IgE antibodies were detected in 29.7% of ADA positive patients. The ADA mean titres (in dilution^{-1}) were not significantly different in patients with and without HRSE: *195 ± 354 vs 128 ± 372*, respectively. Similarly, HRSE positive and negative patients did not display different specific anti-IGF-1 IgE mean titres (in kIU/L): *0.49 ± 0.84 vs 0.44 ± 0.73*, respectively. Furthermore, the occasional and temporary appearance of HRSE during treatment was associated with the presence of anti-IGF-1 IgE only in 40% of cases.
Conclusions: No correlation between the occurrence of HRSE and total ADA titres or anti-IGF-1 IgE antibody levels has been observed.

P1-d3-406 GH and IGF Physiology and Treatment 3

Effects of the two-year treatment with recombinant IGF-1(rhIGF-1) of children with primary IGF-1 deficiency in Poland: a multicenter study

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Background: In 2009 in Poland a therapeutic programme was set up for children with severe primary IGF-1 deficiency (sIGF-1d).
Objectives and hypotheses: The study aim was to evaluate the effects of the first 2 years of therapy with rhIGF-1 on growth velocity of children with sIGF-1d.
Population: Study group comprised 27 children (22 boys) who met the criteria of sIGF-1d - normal GH secretion in three consecutive tests, height < - 3SD and IGF-1 concentration < -2.5 SD in reference to age and sex. Their mean age at the start of rhIGF-1 treatment was 10.06 (min 2.8, max 16.2) years.
Results: Ht SDS at the beginning of treatment was -3.52, maximal peak of GH was 24.37 ng/ml (min:10.7 ng/ml, max: 50.1ng/ml), mean IGF-1 before treatment -2,7SD, mean bone age delay -26 months, Tanner stage 1st in 25 and 2nd in 2 children. After 12 months of treatment mean HT SDS decreased to -3.03 (+ 0.49 SD), and to -2.79 (+0.73 SD) during the second year. Mean Ht velocity before therapy was 4.53 cm/year, 7.84 cm/year (n=23) (max. 8.64cm min. 6.0cm) during the first year and to 6.3cm/year (n=14) during the second year of treatment. The mean dose of rhIGF-1 at the start of treatment was 40 µg/kg bid, increased to 80 µg/kg bid (min 60µg; max 120µg) after 12 months, and to100ug/kg bid (min 80µg, max 120µg) after 24 months. The following side effects were observed: hypoglycaemias (7.41%), headaches (3.7%), others: (18.52%) including: adenoid tissue hypertrophy, heir loss, worsening of scoliosis,local lipohypertrophy in the injection spot.
No mutations in the sequences coding for GHR, IGF-I and STAT5 were found in analyzed 3/27 individuals.
Conclusions:
1. Therapy with rhIGF-1 in short children with severe primary IGF-1 deficiency significantly increased their growth velocity.
2. During the two-year observation period mild adverse effects of the therapy may appear.

P1-d3-407 GH and IGF Physiology and Treatment 3

Ten years after the United States Food and Drug Administration (USFDA) approval of GH treatment for idiopathic short stature (ISS): who is being treated and what is the response to treatment?

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Background: The controversial 2003 USFDA approval of GH for ISS raised concerns for potential inappropriate use.
Objective: To compare characteristics of GH-treated children with ISS vs GHD before & during treatment.
Methods: From ~8000 US children followed in a global GH observational study (GeNeSIS) we compared data for 711 with ISS (77% Caucasian; 73% male) vs 925 with GHD (80% Caucasian; 75% male) who were naive to GH at baseline & had ≥2y GH.
Results: As a percent of total pts with investigator-provided diagnosis of ISS or GHD, ISS increased from 14% in 2002 (year preapproval) to 43% in 2004 (year postapproval) & was 35% overall. At baseline ISS pts were significantly older, shorter, thinner, had shorter parents, higher IGF-I & higher peak GH than GHD pts.

Variable	ISS (n=711), mean±SD	95% confidence limits	GHD (n=925), mean±SD	95% confidence limits
Baseline age (yr)	11.4±2.9	11.2, 11,6	10.7±3.7	10.5, 10.9
Baseline bone age (yr)	10.3±2.9	10.1, 10,6	9.5±3.4	9.3, 9.8
Baseline height SDS	-2.34±0.73	-2.40, -2.29	-2.16±0.97	-2.22, -2.10
Mid-parental height SDS	-0.48±0.76	-0.54, -0.42	-0.26±0.87	-0.32, -0.20
Baseline BMI SDS	-0.61±1.40	-0.71, -0.51	-0.25±1.68	-0.36, -0.14
Baseline peak GH (µg/L)	17.1±15.1	15.9, 18.3	8.2±7.9	7.7, 8.7
Baseline IGF-I SDS	-2.4±1.8	-2.7, -2.1	-3.0±2.1	-3.3, -2.8
1st-yr height SDS gain	0.54±0.32	0.52, 0.56	0.62±0.49	0.59, 0.65
2nd-yr height SDS gain	0.34±0.33	0.32, 0.37	0.40±0.39	0.38, 0.43

[ISS vs GHD at baseline, 1yr & 2yrs]

Both groups showed catch-up growth after 1yr & 2yr GH, but with somewhat less robust response in ISS, despite slightly higher GH dose (0.33 vs 0.31 mg/kg/w). For the subset of pts with data available, 4th-yr height SDS gain & attained height SDS were 0.15±0.34 & -1.1±0.8 for ISS (n=234) vs 0.20±0.31 & -0.7±1.1 for GHD (n=328). GH was discontinued for adverse events for 0.6% ISS vs 1.1% GHD.
Conclusions: Enrollment of US children with ISS in GeNeSIS increased after the 2003 USFDA approval of GH for ISS; these pts are somewhat shorter & older than GHD pts & respond somewhat less well to GH. The data suggest that US pediatric endocrinologists select children for GH treatment based on growth data rather than GH test results.

P1-d3-408 GH and IGF Physiology and Treatment 3

Sleep-related breathing disorders in patients with Prader-Willi syndrome depending on period of growth hormone treatment

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Background: Both central and obstructive sleep apneas are commonly present in patients with Prader-Willi syndrome (PWS). Growth hormone (GH) treatment is reported to improve breathing function in PWS, but the findings are not explicit.

Objective and hypotheses: The aim of our study was to assess the sleep-related breathing disorders in PWS patients before and after initiating of GH treatment, in patients on GH therapy for a longer period and in patients excluded from GH therapy due to severe obesity.
Methods: We used Porti 6 as screening polysomnography (PSG), assessing nasal respiratory flow, respiratory effort, blood oxygen saturation that allows determine apnea-hypopnea index correlated with desaturation per hour (AHI, normal range 0-1) and differentiate central and obstructive sleep apneas (OSA). We present the initial results of the study.
Results:
Group 1- before GH therapy (n=10, age 0,6-8,4 yrs, med 1,5 yrs). PSG was repeated after starting GH therapy in 0,6-2,8 yr (med 0,8 yr) in 7 patients. GH dose was 0,13-0,19 mg/kg/week. Median AHI was 2,6 (OSA- med 37%, hypopneas- med 40%) in the first PSG and 6,2 (OSA- med 62%, hypopneas- med 24%) in the second PSG, p< 0,05.
Group 2- on GH treatment, most patients for >2 yrs (n=17, age 2,9-17,7 yrs, med 7,1 yrs). GH dose was 0,1-0,21 mg/kg/week, median AHI was 4,3 (OSA- med 24%, hypopneas- med 40%).
Group 3- without GH therapy due to severe obesity (n=9, age 4-17,9 yrs, med 14,8 yrs, BMI 19,1-39,4, med BMI 33,8). Median AHI was 4,2, (OSA- med 10%, hypopneas- med 60%).
Conclusions: According to the initial results of our study the sleep apneas seems to deteriorate after short term GH therapy. The results in the group treated with GH for a longer period were better, but seems to not differ from the group not treated with GH. Obstructive sleep apneas and hypopneas dominated among the sleep-related breathing disorders.
The study is sponsored by The Children's Memorial Health Institute, grant number S108/2009.

P1-d3-409 GH and IGF Physiology and Treatment 3

Impact of age at the onset of growth hormone treatment on weight status at the end of treatment in children with idiopathic growth hormone deficiency

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Background: We have reported that 1-year growth hormone (GH) treatment normalizes weight status in children with IGHD (increase of BMI in underweight children and decrease of BMI in overweight children).
Objective and hypotheses: We hypothesize that onset of GH treatment before the age of 8 years is more frequently associated with normalization of weight status in under- and overweight IGHD children compared to IGHD children starting treatment with GH ≥8 years of age.
Methods: We studied change of weight status in 2643 IGHD children from the KIGS® database (61% boys) between onset and end of GH treatment at near final height. Underweight was defined by BMI < 10th percentile, overweight by BMI >90th percentile.
Results: Under- and overweight IGHD children normalized their weight more frequently if treatment was initiated < 8 years than if ≥8 years (Table). In a multiple linear regression , change of BMI-SDS was significantly negatively associated to weight status at onset of GH treatment (p< 0.0001), age at onset of GH treatment (p< 0.0001), years on GH treatment (p=0.0001), and mean GH dose/kg/week (p=0.048).
Conclusions: Our findings support early onset of GH treatment not only to reach the optimal final height but also to achieve normal-weight status in IGHD children. However, normal-weight IGHD children with onset of GH treatment < 8 years were more frequent overweight at end of treatment compared to onset of treatment ≥8 years. Besides an unexpected side- effect of GH, this finding may be explained by the observations in Europe and U.S., that the number of overweight children is gaining with increasing age.

	Underweight		Normal-weight		Overweight	
onset of GH treatment	<8y	≥8y	<8y	≥8y	<8y	≥8y
number	194	339	794	1090	96	130
underweight at end of GH treatment (%)	28	47	8.4	8.2	1	0
normal-weight at end of GH treatment (%)	65	53	73	82	55	38
overweight at end of GH treatment (%)	6.7	0.3	19	10	44	61
p-value	p<0.0001		p<0.0001		p<0.0001	

[Change of weight status during GH treatment]

P1-d3-410 GH and IGF Physiology and Treatment 3

Predictors of growth hormone (GH) responsiveness during transition from childhood to adult GH treatment

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Background: Marked inter-individual variations in IGF-I responses to GH replacement are observed in adults, however little data are available during transition.
Objective and hypotheses: To identify independent predictors of IGF-I response during transition
Methods: From the KIMS database (Pfizer International Metabolic Study), 310 (180 men) patients, (age 21.23±2.53 yrs) with childhood-onset disease treated with GH during transition (age 15-26 yrs) were identified. 'IGF-I response' was estimated from increments in IGF-I SDS, and was adjusted for GH dose corrected for surface area. Body composition was assessed by bio-impedance in 146 patients.
Results: IGF-I levels increased from -3.75±1.94 SDS to -1.36±1.86 SDS on GH treatment (0.51±0.28 mg/day). 'IGF-I response' was negatively associated with female gender (r=-0.21, p=0.0002), and IGF-I SDS at baseline (r=-0.24, p< 0.0001), and positively correlated with BMI SDS (r=0.12, p=0.038), waist circumference (r=0.20, p=0.0015), and additional pituitary hormonal deficiencies (r=0.12, p=0.0015). However, sex hormone treatments, aetiology and age of onset of disease, and lean body mass (LBM) and fat mass at baseline were not related. A regression model which included these variables identified age, gender, BMI SDS and baseline IGF-I SDS as independent predictors of IGF-I response, and explained 22.4 % of the variance. IGF-I response was also related to increases in LBM (r=0.19, p=0.003) and HbA1c (r=0.15, p=0.031), over the first year of treatment, but was not associated with changes in fat mass and fasting glucose.
Conclusions: Our findings of associations between age, gender and BMI, and the IGF-I response during transition suggest that these factors should be considered in GH dose titration to achieve optimal GH replacement. The relationship between IGF-I response and therapeutic endpoints such as LBM indicate that poor responders need particular attention as to dose titration to maximise the benefits of GH therapy.

P1-d3-411 GH and IGF Physiology and Treatment 3

Eight years of growth hormone treatment in children with Prader-Willi syndrome: maintaining the positive effects

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Background: The most important reason for treating children with Prader-Willi Syndrome (PWS) with GH is to optimize their body composition.
Objective and hypotheses: The aim of this ongoing study was to determine whether long-term continuous GH treatment can counteract the clinical course of increasing obesity in PWS by maintaining the improved body composition brought during early treatment.
Methods: In our multicenter prospective cohort study, we have been following sixty prepubertal children for 8 years of continuous GH treatment (1 mg/m^2/day), and used the same dual-energy x-ray absorptiometry (DXA) machine for annual measurements of lean body mass (LBM) and fat percentage (%).
Results: After a significant increase during the first year of GH treatment ($P \leq 0.0001$), LBM remained stable for 7 years at a level above baseline ($P \leq 0.0001$). After a significant decrease in the first year, fat% SDS and body mass index (BMI) SDS remained stable at a level not significantly higher than at baseline ($P = 0.06$, $P = 0.14$, resp.). However, BMI $SDS_{Prader\text{-}Willi\ Syndrome}$ is significantly lower after 8 years of GH treatment than at baseline ($P \leq 0.0001$). After 8 years of treatment height SDS and head circumference SDS had completely normalized. IGF-I SDS increased to + 2.36 SDS during the first year of treatment ($P \leq 0.0001$) and remained stable since then. GH treatment did not adversely affect glucose homeostasis, serum lipids, blood pressure and bone maturation.
Conclusions: This 8-year study demonstrates that GH treatment is a potent force for counteracting the clinical course of increasing obesity PWS.

P1-d3-412 GH and IGF Physiology and Treatment 3

Secondary IGF-I deficiency as a prognostic factor of growth hormone therapy effectiveness in children with isolated, non-acquired growth hormone deficiency

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Background: In recent years, growth hormone (GH) deficiency (GHD) has been classified as secondary IGF-I deficiency. However, the main tool for diagnosing GHD are still GH stimulating tests.
Objective and hypotheses: The aim of the study was to compare the effectiveness of GH therapy in children with isolated, non-acquired GHD and either decreased or normal IGF-I secretion.
Methods: The analysis comprised 300 children with isolated, non-acquired GHD, diagnosed on the basis of GH peak below 10 ng/ml in 2 stimulating tests, who completed GH therapy and attained final height (FH). In all the patients IGF-I concentration was measured before treatment and IGF-I SDS for age and sex was calculated. Secondary IGF-I deficiency was confirmed if IGF-I SDS was low, i.e. below -1.0. Selected auxological indices were assessed at therapy onset (patients' age, H_0SDS - patients' height SDS, BA/CA - bone age delay with respect to chronological age) and after its completion (therapy duration, FHSDS - final height SDS, ΔHSDS - improvement of FHSDS vs H_0SDS).
Results: Better FH together with better ΔHSDS was observed in the patients with decreased IGF-I secretion before treatment, independently from very similar initial deficit of height and despite higher GH peak in stimulating tests and shorter therapy duration than in the group of patients with normal IGF-I secretion. For detailed data see Table 1.

IGF-I before treatment	Low (IGF-I SDS <-1.0)	Normal (IGF-I SDS≥-1.0)	p
Number of patients	173	127	
Age at therapy onset [yrs]	12.6±2.7	11.5±3.6	0.013
H_0SDS	-3.07±0.78	-3.11±0.77	0.633
GH peak [ng/ml]	8.8±5.6	7.2±2.6	0.028
Therapy duration [yrs]	4.7±2.6	5.7±3.2	0.017
FH SDS	-1.42±0.90	-1.74±0.86	0.004
ΔHSDS	1.64±1.01	1.32±1.05	0.010

[Table 1]

Conclusions: Secondary IGF-I deficiency turned out to be an important prognostic factor of better effectiveness of GH therapy in children with isolated, non-acquired GHD.

P1-d3-413 GH and IGF Physiology and Treatment 3

Evaluation of serum IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio in children with growth hormone deficiency (GHD), Turner syndrome (TS) and small for gestational age (SGA) on rhGH treatment

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Background: Surveillance of serum IGF-I throughout rhGH treatment has become a fundamental tool to ascertain compliance and safety. However, IGF-I/IGFBP-3 molar ratio is not usually investigated.
Aim: To evaluate serum IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio in children on rhGH treatment.
Methods: Retrospective, descriptive study of IGF-I and IGFBP-3 concentration in children throughout the first two years of rhGH treatment. IGF-I and IGFBP-3 (ICMA, Siemens) were measured in 28 GHD children (70 samples), 11 TS (27 samples), 12 SGA (31 samples). rhGH median; range dose (mg/kg/week): GHD: 0.19; 0.14-0.24; ST and SGA: 0.30; 0.27-0.33. Results are expressed as SDS according to local data.
Results: The table shows IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio values. IGF-I significantly increased with treatment in GHD and TS (ANOVA: $p < 0.001$) and in SGA group (ANOVA: $p < 0.05$). Although IGFBP-3 and IGF-I/IGFBP-3 molar ratio showed an increase in all 3 groups on treatment, they did not reach statistical significance. A higher proportion of IGF-I and IGFBP-3 samples >+2SD was observed in ST and SGA versus GHD (Chi^2 test: $p < 0.05$). Only 4 samples presented IGF-I/IGFBP3 ratio values >+2SD on rhGH (3 GHD and 1 SGA).
Conclusion: GHD children on standard rhGH have IGF-I and IGFBP-3 profile within normal range, whereas a striking proportion of TS and SGA had IGF-I and IGFBP-3 higher than 2SD. Since most IGF-I/IGFBP-3 molar ratio values on these patients were within normal range, we highlight the importance of adding this index to the surveillance of rhGH treatment.

Mean±SD	IGF-I SDS (samples of > +2,0 SDS)			IGFBP-3 SDS (samples of > +2,0 SDS)			Molar Ratio SDS (samples of > +2,0 SDS)		
*p<0.05 vs basal **p<0.01 vs basal	Basal	1st year	2nd year	Basal	1st year	2nd year	Basal	1st year	2nd year
GHD	-3.06 ±1.96	-0.58 ±2.07** (9%)	-0.00 ±1.89** (9%)	-1.09 ±2.05	-1.08 ±2.22 (9%)	-0.93 ±1.68 (0%)	-0.98 ±1.84	0.19 ±2.1 (9%)	0.49 ±0.43 (12%)
TS	-0.79 ±2.13	1.48 ±1.28** (36%)	2.17 ±1.19** (83%)	-0.23 ±2.37	1.01 ±3.12 (63%)	1.35 ±1.39 (40%)	-0.47 ±0.87	0.59 ±0.82 (0%)	0.70 ±0.87 (0%)
SGA	-0.11 ±0.94	1.37 ±1.03* (44%)	0.89 ±1.49 (33%)	0.16 ±1.15	0.96 ±0.89 (25%)	1.43 ±0.76 (17%)	-0.44 ±0.65	0.41 ±0.88 (0%)	0.19 ±1.06 (10%)

[IGF-I, IGFBP-3 & IGF-I/IGFBP-3 molar ratio values.]

P1-d3-414 GH and IGF Physiology and Treatment 3

Poor growth response and responsiveness to growth hormone therapy in children with growth failure

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Background: The purpose to treat short children with growth hormone (GH) is mainly to achieve a normal stature during childhood and to improve final adult height. However, not all children that are treated will benefit from this therapy.
Objective and hypotheses: To determine the proportion of poor response and responsiveness to first year GH therapy in prepubertal children with idiopathic short stature (ISS), idiopathic growth hormone deficiency (iGHD) and born small for gestational age (SGA) using different criteria.
Methods: Height data at start and after one year of GH therapy, registered in the National Database of the Belgian Study Group for Pediatric Endocrinology, were retrieved from 281 prepubertal children (150 SGA, 26 ISS, 105 iGHD). Criteria for poor response were first-year change in height (ΔHt)SDS and growth velocity (GV) SDS. Poor responsiveness was assessed by GV SDS of the first year on GH response according to Ranke et al. and relative differences between observed and predicted GVs (KIGS prediction models), expressed in terms of studentized residuals (SR).
Results: For all patient groups, ΔHt SDS< 0.5 is a very strict criterion, giving the highest proportion of poor responders (38% in SGA and ISS, 25% in iGHD). The response criteria ΔHt SDS < 0.3 and GV SDS < 0.6 for age and sex generate a comparable amount of poor responders (12-18%). The criteria SR< -1 and GV< -1 SD of the first year on GH response give a similar amount of poor responsiveness (11-18%). We observed a very strong correlation between the traditional response parameters (ΔHt SDS and GV SDS)(R≈0.93) and between the responsiveness parameters (SR and GV SDS) (R≈0.88). When comparing response parameters with responsiveness parameters, a strong correlation also exists (R≈0.78).
Conclusions: In our national registry around 15% of GH treated children (SGA, iGHD, ISS) show a poor first-year response and/or responsiveness by most criteria. ΔHt SDS < 0.5 is a more severe criterion.

P1-d3-415 GH and IGF Physiology and Treatment 3

Quality of life after growth hormone treatment in young adults with isolated GH deficiency

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Background: It is generally accepted that a main goal of any medical treatment is improving quality of life. Few and conflicting data are available on quality of life (QoL) and the psychosocial status of adults treated with growth hormone (GH) during childhood.
Objective: To assess QoL among young adults treated with GH during childhood for GH deficiency (GHD) and other non-GHD conditions.
Methods: SF36 questionnaire was sent to 3523 Italian young adults who underwent GH therapy during childhood. 772 questionnaires of QoL were filled in (21% of total sent questionnaires and 46% of questionnaires actually arrived to the receivers) and assessed using the Medical Outcome Study Short Form 36.The age range of responders was 18 to 44 years. SF-36 contains eight domains: general health (GH), physical functioning (PF), limitations on usual role-related activities due to physical health problems (RP), bodily pain (BP), energy and fatigue (VT), limitations on usual role-related activities due to emotional or mental problems (RE), social functioning (SF), and emotional or mental health (MH). Scores for all eight subscales range from 0 to 100, with higher scores indicating better health or function. The SF-36 scores of the study population were compared to Italian population reference values for gender and age. The differences among groups were assessed by ANOVA OneWay.
Results: The scores of the whole study population were subdivided by gender and age (18-24 yr, 25-34 yr, 35-44 yr) and showed no significant difference among the different diagnostic groups. GH and SF scores were significantly lower in the whole population of GH treated subjects compared with national reference values in any age range (p< 0.05). In particular, subjects with isolated GHD (n=548) showed significantly lower GH and SF scores when compared to healthy Italian population (p< 0.05).
Conclusions: Our findings show that quality of life is partially impaired in young adults treated with GH during childhood.

P1-d1-416 Glucose Metabolism 1

Long-term changes of visual evoked potentials in children and adolescents with type 1 diabetes mellitus

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Background: CNS impairment is common in diabetic patients even in the early stages of the disease and could be associated with peripheral neuropathy.
Objective and hypotheses: To investigate the changes of central nerve conduction in children and adolescents with type 1 diabetes prospectively using visual evoked potentials (VEP) and to know how those results were related to clinical risk factors and parameters of peripheral nerve conduction studies (NCS).
Methods: A total of 75 diabetic patients (29 males) aged 5-26 years (mean 14.3±4.7) underwent VEP and NCS annually for 5 years. For comparison, 52 healthy children were studied.
Results: Out of 75 patients, 33 patients completed annual studies for 5 years. The latencies of P100 were prolonged at the study entry when compared with controls (P< 0.001). Significant positive correlations were found between the VEP latency and glycosylated hemoglobin levels (P< 0.05). The values of latency and amplitude were inversely related to the age of patients and the duration of the disease (P< 0.05). The values of latency were not related to all parameters of NCS.

	Clinical characteristics					Latency (ms)		Amplitude (μV)	
	N (Male)	Age at DM onset (yr)	Age at exam (yr)	Duration of DM (yr)	HbA1C (%)	Right	Left	Right	Left
Control	52 (37)		15.4 ±6.2			101.0 ±5.1	101.7 ±3.9	9.0 ±5.1	8.5 ±4.5
Initial study	75 (29)	10.2 ±3.7	14.3 ±4.7	4.1 ±4.6	10.6 ±3.0	114.4 ±13.5*	113.9 ±13.1*	8.2 ±4.0	8.1 ±3.4
1st yr FU	63 (24)	10.2 ±3.8	15.4 ±4.5	5.2 ±4.5	9.2 ±2.4	109.4 ±10.9	109.3 ±11.4	7.7 ±3.7	7.7 ±3.4
2nd yr FU	50 (19)	9.9 ±3.9	16.3 ±4.6	6.4 ±4.6	9.4 ±2.3	110.0 ±11.5	108.6 ±8.8	7.1 ±2.9	7.5 ±2.8
3rd yr FU	39 (17)	9.5 ±3.9	17.3 ±5.1	7.8 ±5.0	9.6 ±2.5	110.1 ±10.6	109.0 ±11.9	6.3 ±2.4	6.7 ±2.6
4th yr FU	34 (15)	9.3 ±3.8	18.9 ±4.9	9.6 ±4.7	9.9 ±2.4	115.2 ±13.4	114.5 ±13.4	7.2 ±2.6	7.2 ±3.1
5th yr FU	33 (15)	9.2 ±3.9	20.1 ±5.0	10.9 ±4.6	9.6 ±2.4	113.2 ±10.8	111.3 ±10.3	6.6 ±2.9	6.6 ±2.7

[Table 1]
* P< 0.001 between control and initial study.

Conclusions: Poor glycemic control proved to be an important risk factor over 5 years as related to the development of subclinical central neural pathway abnormality. VEP could be considered as a valid noninvasive tool for detecting early diabetic central conduction abnormalities such as retinopathy or optic neuropathy in children and adolescents with type 1 diabetes.

P1-d1-417 Glucose Metabolism 1

Gut microbiota in children with type 1 diabetes differs from healthy children: a case-control study

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Background: A recent study using a rat model found significant differences at the time of diabetes onset in the bacterial communities responsible for type 1 diabetes modulation. We hypothesized that type 1 diabetes in humans could also be linked to a specific gut microbiota. Our aim was to quantify and evaluate the difference in the composition of gut microbiota between children with type 1 diabetes and healthy children.
Methods: Sixteen children with type 1 diabetes and sixteen healthy children were subjected to a case-control study. The fecal bacteria composition was investigated by PCR-denaturing gradient gel electrophoresis and real-time quantitative PCR.
Results: The mean similarity index was 47.39% and 37.56% for the healthy and the diabetic children, respectively, while the intergroup similarity index was 26.69%. In the diabetic children, the bacterial number of Actinobacteria and Firmicutes, and the Firmicutes/Bacteroidetes ratio were all significantly decreased, while the quantity of Bacteroidetes was significantly increased with respect to healthy children. We found a significant increase in the number of Clostridium, Bacteroides and Veillonella and a significant decrease in the number of Lactobacillus Bifidobacterium, Blautia coccoides/E rectale group and Prevotella in the diabetic children. We also found that the number of Bifidobacterium and Lactobacillus, and the Firmicutes/Bacteroidetes ratio correlated negatively and significantly with the plasma glucose level while the quantity of Clostridium correlated positively and significantly with the plasma glucose level in the diabetic group.
Conclusions: This is the first study showing that type 1 diabetes is associated with compositional changes in gut microbiota. These findings could be useful for developing strategies to control the development of type 1 diabetes by modifying the gut microbiota.

P1-d1-418 Glucose Metabolism 1

Development of a prediction model for a "best-fit" basal insulin infusion pattern in children and adolescents with diabetes mellitus type 1 on insulin pumps

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Background: Clinical experience indicates that children with type 1 diabetes on CSII have different needs for basal insulin distribution at different ages (1,2).
Aim: To develop and validate a prediction model for a "best-fit" basal insulin infusion pattern based on 2 independent, very large pediatric patient cohorts.
Methods: Based on the German-Austrian DPV-Wiss database all children on CSII (11/2009) were identified. We excluded 1,248 children from our previous study (1) and retrieved 6,023 new patients (age 10.6 ± 4.3 yrs). Only most recent basal rates were considered. Basal insulin patterns were identified by unsupervised clustering (1). Logistic regression was used to identify the probability for a patient of being assigned to a specific basal insulin pattern. We validated prediction by comparing the previous (1) and current cohort.
Results: 5,903 of the 6,023 children were assigned by clustering to 1 of 4 key basal insulin patterns. 2,490 Patients (42.18%) reflected the oldest group (mean age 12.8 yrs) demonstrating a biphasic "dawn-dusk" pattern. 853 patients (14.45%) were the youngest group (mean age 6.3 yrs) and showed maximum insulin infusion at 9-10 pm. Logistic regression showed that age, in part duration of diabetes and gender predicted basal insulin infusion patterns.
Conclusions: We confirmed the existence of 4 distinct basal insulin infusion patterns in children. Because of the very large cohorts, patterns are likely to approximate real basal insulin needs in these patients. A priori prediction of a "best-fit" basal insulin infusion pattern can contribute to improvement of CSII in children. Moreover, our data is of high potential value for modeling decision corridors of closed loop CSII algorithms (3).
Holterhus et al. 2007, Diabetes Care 30:568-573; Bachran et al. 2012, Pediatr Diabetes 13:1-5; Holterhus et al. 2013, Diabetes Care [Epub ahead of print]

P1-d1-419 Glucose Metabolism 1

Diminished serum estrogenic activity in girls with type 1 diabetes

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Background: Studies in premenopausal women with type 1 diabetes (T1D) have shown that they have an increased risk of cardiovascular mortality and osteoporosis. These data suggests that the physiologic estrogen protection conferred against these diseases is reduced in T1D women.
Objective: To evaluate the overall serum estrogenic activity (EA) in girls with T1D.
Hypothesis: Girls with T1D have diminished serum estrogenic activity.
Population and methods: Girls with T1D (N=51) and healthy controls C (N=45) were studied. Results were analyzed according to pubertal development and presence of menarche. Modified *E-screen* bioassay was developed. This *in- vitro* assay evaluates proliferation of MCF-7 BUS cells, which are known to be estrogen sensitive. Proliferation was assessed by fluorometry (CyQuant® kit). Results are expressed as the response observed relative to a serum pool from healthy women.
Results: *E-screen* bioassay correlated significantly with concomitant serum levels of 17β-estradiol in follicular (r=.55, p=.0001) and luteal phase (r=.67, p=.0001). Serum 17β-estradiol levels were similar in both groups except during follicular phase in postmenarchal girls (T1D=15 and C=26 pg/mL, p=.005). Lower proliferative EA was observed in prepubertal girls with T1D and postmenarchal girls with T1D during the follicular and luteal phase of menstrual cycle (p< .05) (Table). EA was similar in premenarchal pubertal girls of both groups.

	Tanner 1	Tanner 2-3	Tanner 4-5 Premenarchal	Tanner 4-5 Follicular Phase	Tanner 4-5 Luteal Phase
T1D	57.7±11 (N=8)*	84.6±32 (N=20)	96.4±24 (N=5)	81.6±10 (N=18)*	91.2±31 (N=18)*
C	74.9±16 (N=9)*	80.5±13 (N=16)	98±27 (N=9)	96.7±25 (N=11)*	123.9±35 (N=11)*

[Estrogenic Activity]

Conclusion: This is the first report of a lower EA in serum of T1D girls which may play a role in the loss of physiologic estrogen protection against cardiovascular disease in women with T1D. This may be due to a lower estrogen activity of the mix of estrogens metabolites. (Fondecyt 1100123).

P1-d1-420 Glucose Metabolism 1

Retinal thinning in young patients with type 1 diabetes mellitus: is it the first sign of diabetic retinopathy?

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Background: Central retinal thinning, was reported as the earliest sign of diabetic retinopathy (DR).
Objective: This study aims to compare retinal thickness, in diabetic patients with normal fundus photography and matched healthy controls. Furthermore we evaluate the effect of metabolic control, disease duration and autoimmune biomarkers on retinal thickness (CRT).
Methods: We investigated 74 T1D patients (41 boys) in treatment with insulin MDI or CSII with median *(IQR)* age 14.5 *(6.3)* years, disease duration 5.4 *(4.1)* years, last year HbA1C and insulin requirement respectively 7.9 *(1.0)*% and 0.9 *(0.3)* U/Kg/day. None of them had signs of incipient DR and / or nephropathy evaluated by fundus examination and AER. Central retinal thickness was measured by Spectral Domain OCT Topography map (OTI, Toronto, Canada) in foveal area (FA) and in superior (S), temporal (T), nasal (N) and inferior (I) of pericentric and paracentric areas. The patients were tested at disease onset for one or more of these autoantibodies (AAbs): IA2A, GAD65A, Zn8A, IAA, ICA. Retinal thickness was also measured in forty, age and gender matched, healthy controls.
Results: The retina resulted thinner in foveal ($p < .001$) and paracentral areas ($p < .0001$) and thicker in nasal pericentral area ($p < .0001$) in both eyes of diabetic patients compared to controls. CRT was not correlated to metabolic control, blood glucose excursion and disease duration. In the patients tested for at least 3 AAbs (n=26) the number of positive AAbs resulted inversely correlated to retinal thickness in fovea ($p < .001$), N-paracentral ($p < .01$), N-pericentral ($p < .01$) and I-pericentral ($p < .05$) areas.
Conclusions: Our results confirm central retinal thinning in T1DM before appearance of overt DR. The thickening of nasal pericentric area could instead be due to edema caused by early microangiopathy. The relation of retinal thinning with AAbs suggests a possible role of autoimmunity in the pathogenesis of DR.

P1-d1-421 Glucose Metabolism 1

Performance of meglitinide analogues in 117 adolescent patients with HNF1A-MODY (MODY3): experience from the prospective German/Austrian DPV database

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Background: HNF1A-MODY (MODY3) is caused by a heterozygous gene defect of *HNF1A* and is characterized by a progressive loss of glucose-dependent insulin secretion. At present, the use of sulphonylureas (SU) is recommended despite a potential risk of hypoglycaemia. Meglitinide analogues display lower prandial glucose levels and reduced risk of hypoglycaemia than SU.
Objective and hypotheses: Therefore we evaluated the use of megitinides versus established treatment regimens in HNF1A-MODY patients with disease onset before age 18 yrs.
Methods: We studied performance of meglitinides in terms of hypoglycaemia, HbA1c and weight in 117 subjects with HNF1A-MODY and onset < age 18 yrs using the DPV-Wiss database on patients with diabetes from Germany and Austria.
Results: Of the 117 patients with HNF1A MODY, 22 used meglitinides alone or in combination with insulin or other oral medications (summarized in the table).

treatment group n (female)		Meglitinides 22(68%)	No meglitinides 95(62.1%)	p-value
Age at diabetes onset [yrs]		13.2(11.9-14.9)	11.7(9.8-14.8)	0.24
Present age [yrs]		17.2(14.6-19.4)	17.6(14.2-18.5)	0.76
HbA1c %		6.9(6.1-7.9)	7.0(5.9-7.5)	0.67
Severe Hypoglycaemia	(1/100 patientyrs)	0	2.7	0.4
Treatment [%]	lifestyle only	0	29.5	-
	Insulin alone	0	35.8	-
	OADs alone	31.9	18.9	-
	insulin and OADS	40.9	15.8	-
	combinations with SU / metformin	13.6 / 13.6	31.6 / 4.2	-

[HNF1A-MODY patients treated with/without glinides]
OADS= oral antidiabetic drugs

Conclusions: Meglinitides are effective in the treatment of adolescent patients with HNF1A -MODY. In most cases meglitinides are not used alone but combined with insulin or even other oral hypoglycaemic drugs. There is no severe hypoglycaemia if meglitinides are used alone or in combination. This effect was found even as approx. 30% patients without meglitinides were treated without any medication that could cause hypoglycaemia. Thus we suggest meglitinides as oral treatment of first choice also in patients with HNF1A-MODY younger than 18 yrs.

P1-d1-422 Glucose Metabolism 1

The Euro-WABB Registry: analysis of obesity and diabetes prevalence in the first 115 patients affected by Wolfram, Alstrom or Bardet-Biedl syndrome recruited to the registry (www.euro-wabb.org)

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Background, objectives and hypotheses: We aimed to develop a registry for the rare genetic diseases Wolfram (WS), Alstrom (AS), Bardet-Biedl (BBS) and other diabetes syndromes, containing clinical, genetic diagnostic and outcome data in order to establish the natural history of these diseases; to assess clinical management; to characterize cohorts for future clinical trials; and to establish genotype phenotype relations. This abstract describes the first 115 patients recruited.
Methods: Patients who fulfilled diagnostic criteria (genetic) were recruited from both within and beyond Europe by their physicians. Information was collected for 42 'core' data fields, reached by consensus to differentiate be-

tween syndromes. We analysed prevalence of core clinical symptoms including obesity and diabetes.
Results: The median age (range) was 15 yrs (2-54yrs). There were 52 patients with WS (median age 19yrs (range 4-45yrs), 29 with AS (17 yrs (3-54yrs), 31 with BBS (10yrs (2-20), 2 with Wolcott-Rallison and 1 with vision and hearing impairment of unknown cause. The prevalences of obesity and median ages of onset were: WS (1/52; 8yrs); AS (21/29; 1); BBS (25/31; 1yrs); $p< 0.001$ for obesity prevalence WS vs AS and BBS combined). The prevalences of diabetes and median ages of onset were: WS (46/52; 5yrs); AS (9/29; 15yrs); BBS (2/31; 12 yrs); $p< 0.01$ for age of onset WS vs AS and BBS combined.
Conclusions: The core dataset captured sufficient data to differentiate between diabetes syndromes. Diabetes mellitus presented before puberty in WS, was not associated with obesity, and is known to be insulin dependent; whereas it presented during puberty in AS and BBS, was associated with obesity, and is insulin resistant. The prevalence of diabetes is low in AS and BBS during childhood. Further patient recruitment and longitudinal data collection will use a consensus extended dataset of 400 fields to accurately characterize the phenotypes.

P1-d1-423 Glucose Metabolism 1

The gene for a novel syndrome of diazoxide-responsive hyperinsulinaemic hypoglycaemia and polycystic kidney disease maps to chromosome 16

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Background: Hyperinsulinism is an important cause of infancy-onset recurrent hypoglycaemia. Although most patients present with isolated hyperinsulinism, it may also be associated with a number of complex developmental syndromes.
Objective: To characterise clinically a large consanguineous kindred segregating hyperinsulinaemic hypoglycaemia and renal abnormalities and to perform genetic linkage studies in this family.
Methods: Members of the family were subjected to a detailed clinical assessment. Massive whole-genome SNP genotyping (HumanOmni1S Beadchip Kit, Illumina®) was carried out in affected patients and unaffected relatives. Array raw data were analysed using GenomeStudio software by Illumina®.
Results: Four patients presented with mild, transient diazoxide-responsive hyperinsulinaemic hypoglycaemia in infancy. On examination, they also showed enlarged polycystic kidneys and hypertension, but no hepatic cysts. Although renal function was considered normal at presentation, the older patients developed progressive chronic kidney disease over time (one of them, currently aged 22 years, is on haemodialysis). The segregation pattern within the family was consistent with autosomal recessive inheritance. Whole-genome SNP genotyping defined a single, 2.5 Mb region of homozygosity on chromosome 16 common to all affected individuals but none of the unaffected siblings studied, which is likely to encompass the causative gene.
Conclusions: These results suggest that patients in this family suffer from a novel genetic syndrome and provide the basis for identifying the causative mutation(s). Understanding the underlying molecular mechanisms may provide insight into the developmental control of the affected organs.

P1-d1-424 Glucose Metabolism 1

Are environmental and genetic factors at type 1 diabetes diagnosis associated with the development of microvascular complications?

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Background: Putative environmental risk factors for microvascular complications have recently emerged. Infection is associated with increased risk of neuropathy and nephropathy in type 2 diabetes. We have shown that vitamin D deficiency (VDD) is associated with incident retinopathy in type 1 diabetes (T1D).
Objective and hypotheses: To determine if VDD, enterovirus infection (EV) and HLA-DQ haplotype influence glycaemic variability and microvascular complications.
Methods: An incident cohort of 206 T1D patients was recruited April 1997-September 1999. Testing for HLA-DQ haplotype, 25-hydroxyvitamin D level (VDD< 50nmol/L) and EV (stool/plasma) was performed. After minimum duration 2 years, patients were assessed for retinopathy, elevated albumin excretion rate (EAER) and microalbuminuria (MA). Statistical power was 95%, α=0.05 for 150 patients.
Results: At diagnosis, VDD rate was 21%, EV 31% and high-risk HLA-DQ 69%. HbA1c did not differ between those with VDD or EV (p=NS).
Complications assessment was performed in 155 (75%) patients, median 3 visits. At final assessment, median age was16.8 years, IQR [15.5-18.3], HbA1c 8.7% [7.8-9.7] and median duration 9.7 years [6.3-13.0]. Retinopathy was present in 31%, EAER 40%, MA 6.8%. VDD was associated with higher intrapersonal HbA1c SDS (1.2 vs 0.6, p=0.04) but not mean HbA1c. Mean HbA1c and HbA1c SDS did not differ between those with or without EV (p=0.4). Neither EV nor VDD at diagnosis were associated with incident retinopathy, EAER or MA (p=NS). Microvascular complications did not differ between those with high and low risk HLA-DQ haplotypes (p=NS).
Conclusions: VDD at diagnosis is associated with greater glycaemic variability at follow up, possibly by influencing insulin sensitivity. EV and VDD at diagnosis and HLA-DQ risk haplotypes are not associated with the development of microvascular complications.

P1-d1-425 Glucose Metabolism 1

Oleate protects INS1 cells from palmitate-induced apoptosis by down-regulating ER stress and GSK3β through stearoyl-CoA desaturase 1

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Background: The loss of functional β-cell mass, at least in part secondary to increased β-cell apoptosis, is increasingly recognized as one of the main contributing factors to the pathogenesis of type 2 diabetes. Our previous study have identified that endoplasmic reticulum (ER) stress and GSK3β involved in palmitate-induced β-cell apoptosis (lipotoxicity). However, the effect of oleate on β-cell is still controversial.
Objective and hypotheses: The present study investigated whether oleate protected β-cell from palmitate-induced apoptosis and its molecular mechanisms.
Methods: INS1 cells were cultured with varying concentrations of palmitate, oleate, TO-901317 or co-treatment of palmitate with either oleate or TO-901317. Cell viability and apoptosis were measured by CCK-8 assay, Hoechst 33342 / PI, flow cytometric assay and electron microscopy; ER stress and GSK3β activity were assessed by RT-PCR and western blot. We also estimated intracellular triglyceride accumulation through nile red staining and electron microscopy.
Results: Contrary to lipotoxicity of palmitate, 0.25~0.5 mM oleate increased INS1 cells viability ($p< 0.05$). Interesting, we identified that oleate rather than

palmitate induced a significant intracellular triglyceride accumulation ($p< 0.05$).
Furthermore, co-treatment of oleate with palmitate apparently decreased palmitate-induced apoptosis by down-regulating ER stress and GSK3β activity ($p< 0.05$), Besides, we also found that the mRNA level of Stearoyl-CoA Desaturase 1 (SCD1) was up-regulated ($p< 0.05$). Finally, co-treatment of Palmitate with LXR-agonist TO-901317, which directly up-regulated SCD1, also leaded to intracellular triglyceride accumulation and the reduction of ER stress and GSK3β activity ($p< 0.05$).
Conclusion: Oleate protected INS1 cells from palmitate-induced apoptosis by down-regulating ER stress and GSK3β activity throught promotion of appropriate triglyceride accumulation, which related to the up-regulation of SCD1.

P1-d2-426 Glucose Metabolism 2

^{18}F-DOPA PET MRI as a new imaging modality for the precise localisation of focal congenital hyperinsulinism

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Background: Congenital Hyperinsulinism (CHI) includes two major histological subtypes; diffuse and focal. Fluorine-18-L dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET/CT) has been established as a novel imagining technique to differentiate focal from diffuse CHI. However CT provides only limited soft tissue contrast and exposes the patient to a significant radiation dose.
Objective and hypotheses: PET/MRI could provide images with an excellent soft tissue contrast, very good spatial resolution of the anatomy and very accurate temporal and spatial image fusion with no additional radiation exposure. To evaluate the feasibility of using ^{18}F-DOPA PET/MRI for the diagnosis focal CHI.
Methods: 5 children with severe CHI underwent simultaneous ^{18}F-DOPA PET/CT and PET/MRI imaging. All medications including octreotide and glucagon were discontinued 48hours before the scan. The ^{18}F-DOPA was administered intravenously at a dose of 4 MBq/kg and iodine contrast media at a dosage of 1.5 ml/kg. Three regions of interest were drawn in the head, body, and tail of the pancreas to calculate the standardized uptake values (SUV max).
Results: PET/MRI in 4 children revealed diffuse CHI (SUV< 1.3) and one child had focal CHI (SUV>1.5). The focal lesion was delineated clearly in accordance with the results from PET/CT images. In addition PET/MRI provided soft tissue and anatomical information of the adjacent structures that aided the precise surgical resection of the lesion.
Conclusions: In this preliminary study, we have demonstrated the feasibility of using PET/MRI as a novel imaging modality for diagnosing focal CHI. Further studies are needed to establish the accuracy and validity of PET/MRI. Given the potential of less radiation exposure and higher soft tissue clarity, PET/MRI is likely to become a preferred imaging modality for CHI management.

P1-d2-427 Glucose Metabolism 2

Subclinical diabetic cardiomyopathy in children

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Background: T1DM affects cardiac structure and function independent of blood pressure or coronary artery disease due to specific myocardium lesion called Diabetic Cardiomyopathy (DCM). Its develops asymptomatically for a long period of time and causes heart failure in adults.
Objective and hypotheses: The aim of our study is to trace development of cardiomyopathy in children from imperceptible to significant changes in cardiovascular activity and identify features of stages of the pathological process.
Methods: Comprehensive assessment of patients included clinical examination, ECG, heart rate variability, blood pressure, echocardiography, Doppler echocardiography of transmitral blood flow, and nailbed capillaroscopy.
Results: We have examined 80 patients (34 boys and 46 girls) with T1DM (mean age 12.5 ± 0.2 years) with disease duration from up to 12 years, and 30 healthy children of the control group. Correlation analysis of the relationships between echo- parameters, heart rate variability, clinical and other instrumental data allowed us to investigate the dependence of central hemodynamic (CH) on autonomic homeostasis, duration of DM, metabolic control, and signs of other complications. The earliest signs of diabetic heart affection (first stage of DCM) are deterioration of myocardial relaxation in diastole ($\Delta p=0.376 \pm 0.006$), hyperkinetic type of CH, hypertrophic type of left ventricular diastolic dysfunction (LVDD), and dysautonomia. Tachycardia at rest, prevalence of sympathetic heart innervation, left atrial dilation, myocardial tension ($\Delta p = 0.374 \pm 0.009$) and pseudonormal type of LVDD develop with further progression of myocardial degeneration (second stage of DCM). Signs of the third stage of DCM in children are rigid heart rate (> 100 beats per minute), excessive sympathetic activity, dilatation of the left heart chambers, hypokinetic type of CH, low ejection fraction (< 50 %), poor contractility ($\Delta s< 30$ %) and low myocardial tension ($\Delta p = 0.315 \pm 0.002$), along with the restrictive type of LVDD, combined with signs of cardiovascular autonomic nerve dysfunction, microangiopathy, and peripheral neuropathy.
Conclusions: On the basis of our own research and analysis of data of about 500 references, we suggest to distinguish three stages of DCM in children and adolescents with T1DM.

P1-d2-428 Glucose Metabolism 2

Measuring the effect of diabetic ketoacidosis on brain compliance using a non-invasive device

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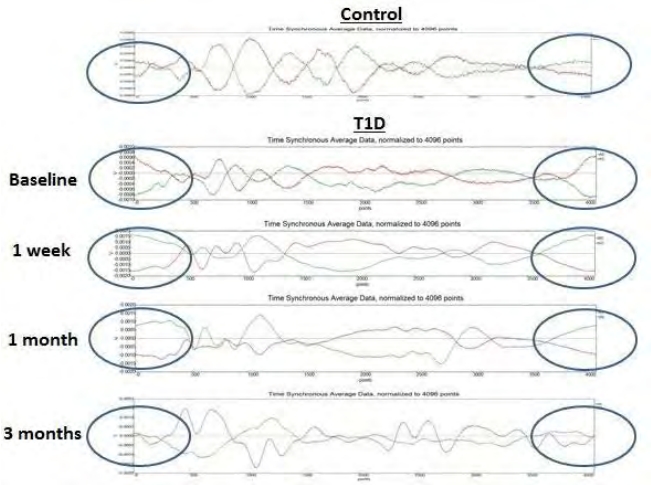
Background: In addition to overt cerebral edema, subclinical brain compliance changes may also occur in diabetic ketoacidosis (DKA). The exact time course of recovery from such changes is unknown. The Nautilus Neurowave System™ (NNS) (Jan Medical), a transcranial accelerometer-based device for measuring brain compliance, may offer a non-invasive means to recognize and elucidate the natural history of subclinical brain compliance changes during and after DKA.
Objective and hypotheses: This pilot study assesses the feasibility of using the NNS to investigate whether or not the cerebral vasculature produces a unique signal in children with DKA and if so, to follow the duration of this signal over time.
Methods: Children 10-17 years, with type 1 diabetes (T1D) within 24 hrs of DKA (defined by PES/ESPE guidelines) and controls wore the NNS to record cerebral blood vessel pulsations for 5 minutes. Subjects then repeated the evaluation 1 week, 1 month, and 3 months later. Data analysis for the NNS was performed in a non-blinded fashion by a trained specialist.
Results: Five T1D and 4 controls were recruited. Subjects completed all visits, except 1 T1D, who was dropped after the 1 week visit due to repeat DKA. A unique signal was visualized in those with DKA that was not seen in controls and the signal diminished over time (Figure 1).
Conclusions: These data were used to train the system and a blinded protocol to detect changes in brain compliance is currently underway. The NNS may be useful for non-invasive measurement of brain compliance during DKA to aid in the diagnosis of cerebral edema and to follow its resolution over time.



[Figure 1: Time-averaged electronic representations of cerebral vascular pulsations. The unique signal appears as widened amplitude at the systole start (left circles) and diastole end (right circles) points. It is only present in the T1D group, persisting through 1 month, but resolved by 3 months.]

P1-d2-429 Glucose Metabolism 2

Diazoxide-responsive hyperinsulinaemic hypoglycaemia caused by a *de novo* novel *HNF4A* mutation

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Background: The phenotypes associated with heterozygous *HNF4A* gene mutations have been recently extended also to diazoxide responsive hyperinsulinemic hypoglycemia (HH) in addition to maturity-onset diabetes of the young (MODY).
Case report: The girl was born at term to healthy parents with no history of diabetes mellitus. Her birth weight was 3800g, birth length 51cm. In the first day of life she displayed severe hypoglycemia (1.3 mmol/L). The mean rate of intravenous glucose administration required for maintaining normal plasma glucose was 13 mg/kg/min. Within the first days of life she developed catheter sepsis. At the age of 5 days, further endocrine investigation was performed: at hypoglycemia (1.8 mmol/L), the insulin level was relatively high (13.3 mIU/L) and capillary beta-hydroxybutyrate was suppressed (0.1 mmol/L). Thus, the diagnosis of hyperinsulinemic hypoglycemia was confirmed. We started the treatment with diazoxide in increasing doses. However, due to a poor effect within the first 2 days the treatment was switched to octreotide administered in 4 daily doses. The glycemia remained in lower normal range on this treatment in combination with intensive maltodextrin diet. Simultaneously, we performed molecular genetic testing of the genes *ABCC8* and *KCNJ11* encoding the K(ATP) channel proteins and *HNF4A* in the proband. Whereas mutations in K(ATP) channel genes were excluded, a causal novel heterozygous mutation (p.Ser73delCCT) within the *HNF4A* was found; this mutation appeared *de-novo*. Therefore, the octreotide treatment was replaced again by diazoxide at the age of 3 months. By the age of 12 months the girl has no episodes of hypoglycaemia and her psychomotor development is normal.
Conclusions: The *HNF4A* gene testing should be considered in patients with hyperinsulinemic hypoglycaemia irrespective of a family history of diabetes once K(ATP) channel mutations have been excluded.
The study was supported by the grant IGA NT 11402.

P1-d2-430 Glucose Metabolism 2

Utilizing bedside ultrasound measurements of optic nerve sheath diameter to assess increased intracranial pressure in children with diabetic ketoacidosis

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Background: Cerebral edema and increased intracranial pressure (ICP) can occur during treatment of diabetes ketoacidosis (DKA). Ultrasound (US) measurements of optic nerve sheath diameter (ONSD) have been used as a marker of cerebral edema in traumatic brain injury but the value of this technology in children with DKA has not been established.
Objective and hypotheses: To determine if bedside US can be used as a non-invasive method to monitor ICP in DKA management.
Methods: 7 T1D patients (3 males; age 9-15 yrs, 4 new onset TID) were enrolled in a pilot study of the feasibility and utility of ONSD in children with DKA. Serial ONSD measurements were obtained during the first 24h of treatment and at hospital discharge (average 4 US/patient). Normal ONSD is ≤4.5 mm in healthy children.
Results: Initial vital signs and laboratory results in the 5 patients with normal ONSD are contrasted with the 2 patients who had ONSD >4.5 mm in the Table. Serum bicarbonate and carbon dioxide had a negative correlation with increased OSND and heart rate had a positive correlation with increased ONSD ($p < 0.05$). ONSD was < 4.5 mm in all patients at discharge.
Conclusions: Serial measurements of ONSD are feasible in children with severe DKA. Increased ONSD correlates with biochemical abnormalities associated with increased risk of cerebral edema in youth with T1D. Further studies utilizing cranial imaging are needed to determine if ONSD can be used as a non-invasive method to monitor pediatric patients for the development of cerebral edema in DKA.

Initial Vital Signs and Laboratory Results	Normal ONSD (mean + SD) (n=5)	Increased ONSD (mean + SD) (n=2)
ONSD Right Eye	3.5 ± 0.03	5.9 ± 0.03
ONSD Left Eye	3.5 ± 0.04	4.9 ± 0.01
Heart Rate (bpm)	118 ± 17	147 ± 8
Blood Pressure (mm Hg)	113/60 ± 5/6	114/62 ± 5/2
Plasma Glucose (mg/dL)	326 ± 241	412 ± 60
pH	7.24 ± 0.16	7.08 ± 0.09
HCO3 (mEq/L)	14.5 ± 6.7	5.7 ± 0.1
pCO2 (mmHg)	28.8 ± 11.56	20.5 ± 3.5

[Clinical Data]

P1-d2-431 Glucose Metabolism 2

Efficacy and safety of closed-loop insulin delivery during reduction or omission of meal boluses in adolescents with type 1 diabetes

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Background: Closed-loop insulin delivery with meal announcement reduces mean glucose and increases time in target in adolescents with type 1 diabetes. However, omission of insulin doses with meals is common in adolescents and might compromise glucose control during closed-loop in the home settings.
Objective and hypotheses: We evaluated the efficacy and safety of closed-loop insulin delivery (CL) during reduction and omission of meal insulin boluses in adolescents with type 1 diabetes.
Methods: A randomised cross-over study compared CL versus conventional pump therapy (open-loop) over a 24h stay at the clinical research facility. Twelve young people with type 1 diabetes on insulin pump treatment (M 6;

age 15.9±1.8 years; total daily insulin dose 0.9±0.3 U/kg/day; A1C 9.2±1.2%; mean±SD) were studied on two occasions. Standardised evening meal (70 g CHO) was given at 19:00, breakfast (50g CHO) at 08:00 and lunch (55g CHO) at 12:30; meals were identical on the two occasions. Meal boluses were calculated using the subjects' pump bolus calculator. The evening meal bolus was calculated for 35g CHO and the bolus for lunch was not delivered. During CL, basal insulin delivery was manually adjusted by a model predictive control algorithm based on real-time sensor glucose.
Results: Plasma glucose levels were within the target range of 3.9-10.0mmol/L for 74 (55,86)% of time during CL and 62 (49,75)% during open-loop; median (IQR), p=0.26, rank test. Time spent above 10mmol/l [23 (13,39) vs 27 (10,50)%, p=0.88] or below 3.9mmol/L [1 (0,4) vs 5 (1,10)%, p=0.24] and mean glucose [8.0 (7.6,9.3) vs 7.7 (6.6,10.1)mmol/L, p=0.79] were also similar. Plasma glucose after evening meal was 7.5 (6.6,8.5) vs 6.1 (3.8,9.7) mmol/L, and after lunch 7.6 (7.0,8.4) vs 9.5 (7.8,14.0)mmol/l.
Conclusions: Closed-loop delivery can be applied safely to control glucose levels in adolescents with type 1 diabetes miscalculating or missing meal insulin boluses.

P1-d2-432 Glucose Metabolism 2

A mutation in the ABCC8 gene (c.1773delC) causing congenital hyperinsulinaemia evolving into postprandial hyperglycaemia

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Background: There have been reports of congenital hyperinsulinism evolving into diabetes mellitus later in life; most well-known being carriers of the E1506K mutation in the ABCC8 gene (Huopio H. et al. J Clin Invest. 2000;106:897). Proposed mechanisms include apoptotic death of insulin-overproducing beta cells possibly caused by constant calcium-influx into the cells. However, it is uncommon for patients with congenital hyperinsulinism to develop diabetes mellitus unless they undergo pancreatectomy.
Subjects: Two unrelated Japanese patients with neonatal-onset congenital hyperinsulinism who developed postprandial hyperglycemia at the age of 11 and 16, respectively. Even after meeting the criteria of diabetes mellitus, both patients presented with concurrent fasting hypoglycemia making clinical management more difficult.
Methods: Mutational analysis was performed by PCR amplification and direct sequencing of all exons of the ABCC8 and the KCNJ11 gene. To detect deletions of the exons, MLPA analysis of the ABCC8 gene was also performed. Oral glucose tolerance tests were performed by the standard procedure.
Results: A mutation in the ABCC8 gene (c.1773delC, p.F591fs604X) was identified in both patients. In addition, one of the patients had another mutation (p.R1420H) of the ABCC8 gene. No mutations were identified in the KCNJ11 gene. Findings of OGTT were similar for both patients, i.e, marked postprandial hyperglycemia with 120 min glucose of 13.76 mmol/L and 12.21 mmol/L, respectively. Thereafter, they developed hypoglycemia with continued secretion of inappropriately high insulin for glucose. Electrophysiological analyses using mutant plasmids and patch-cramp experiments are currently underway.
Conclusions: Our cases might provide additional evidence that certain inactivating KATP channel mutations might confer susceptibility to develop diabetes mellitus later in life.

P1-d2-433 Glucose Metabolism 2

Pancreatic enzyme supplementation slows gastric emptying and improves post prandial glycaemia in adolescents with cystic fibrosis

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Background: As life expectancy increases in cystic fibrosis (CF), CF related diabetes (CFRD) is becoming more prevalent. Early carbohydrate intolerance precedes CFRD, and is marked by postprandial hyperglycaemia. Gastric emptying is central to postprandial blood glucose homeostasis and determines overall glycaemic control. Fats require lipolysis in order to stimulate small intestinal feedback that slows gastric emptying. Pancreatic enzyme replacement therapy (PERT) improves fat digestion.
Objective: To determine the effect of PERT on gastric emptying and postprandial glycaemia in adolescents with CF.
Hypothesis: Rapid gastric emptying of a high fat meal in CF results in postprandial hyperglycaemia, which will be ameliorated by PERT.
Methods: We conducted a randomised double blinded cross over trial in 14 adolescents (age 13.1 ±2.7, BMI 19.6 kg/m^2 ±2.8, 2/14 with CFRD) with pancreatic insufficient CF. Subjects consumed a ^{13}C labelled high fat pancake on 2 occasions, with Creon Forte (50,000IU) or placebo. Gastric emptying was measured by ^{13}C breath test. Blood was sampled frequently over 4 hours for blood glucose concentrations. Seven age and sex matched controls were also studied (without PERT).
Results: Gastric emptying was slower after PERT than placebo (half-emptying time 185.2 ±108.4 minutes vs 120.0 ±170.9 minutes, p = 0.03), while post prandial glycaemia was less after PERT (p = 0.03), but failed to normalise in 6 subjects (Table 1). Delayed gastric emptying correlated with improved post prandial glycaemia (r = -0.6, p 0.008).

	Median glucose AUC 0-120minutes (mmol/Lmin)	Comparison to controls (p value)
Controls	609.6 ± 68.9	
CF subjects + PERT	778.0 ± 123.3	0.006
CF subjects + placebo	852.2 ± 182.2	0.0006

[Glucose area under the curve (AUC) 0-120minutes]

Conclusion: In pancreatic insufficient adolescents with CF, PERT slows gastric emptying and improves post prandial hyperglycaemia.

P1-d2-434 Glucose Metabolism 2

Whole genome SNP genotyping and exome sequencing reveal novel genetic variants and putative causative genes in congenital hyperinsulinism

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Background: Congenital hyperinsulinism of infancy (CHI) is a rare disorder characterized by severe hypoglycaemia due to inappropriate insulin secretion. CHI genetic bases involve defects in key genes regulating insulin secretion from pancreatic β-cells. In particular, recessive inactivating mutations in *ABCC8* and *KCNJ11* genes are the most common cause of CHI. Despite the advances in understanding the molecular pathogenesis of CHI, specific genetic determinants in nearly 50% of the CHI patients remain unknown, suggesting additional locus heterogeneity.
Objective: To search for novel loci contributing to the pathogenesis of CHI.
Methods: We performed a family-based association study using transmission disequilibrium test on 17 CHI patients lacking mutations in *ABCC8*/*KCNJ11* genes. By TDT analysis, we identified 51 genes with a significant association with the disease. Moreover, we applied whole exome sequencing analysis on 10 probands having different clinical phenotypes and we obtained hundreds of single nucleotide coding variations per sample.
Results: Applying a prioritizing strategy of exome variants, we identified potential causative mutations in 17 genes implicated in the regulation of insulin secretion (*KCNH6, GNAS, ACACB, NOTCH2, RYR3, TRPV3, TRPC5, CAMK2D, PIK3R3, CDKAL1, SCN8A, KCNJ10, PDE4C, NOS2, SLC24A6, CACNA1A, PC)* and four TDT associated genes (*SLC37A3*, *CSMD1*, *SULF1*, *TLL1*). Using exome sequencing approach as a diagnostic tool for CHI, in four with no pre-screening genetic analysis, we found mutations in three CHI causative genes (*ABCC8*, *GLUD1 and HNF1A).*
Conclusions: Overall, our study indicates novel candidate genetics variants and it should be considered as a starting point for further molecular characterization of the identified mutations and for widening the study on a larger number of CHI patients grouped for clinical phenotype.
Grant support: PRIN2006063299 and PRIN2008WY2TY9.
Multi-center Italian CHI registry made possible the enrolment of HI families.

P1-d2-435 Glucose Metabolism 2

Molecular analysis of congenital hyperinsulinism (CHI): genotype/phenotype correlations

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Background: CHI is a clinically, genetically and histologically highly heterogeneous entity. Mutations in *ABCC8* and *KCNJ11* represent the most frequent molecular defect.
Objective: Molecular diagnosis and genotype-phenotype correlations in 11 patients with a clinical CHI diagnosis.
Methods: Diagnosis was based on nonketotic hypoglycemia, in the face of detectable insulin, decreased free fatty acids, hyperresponse to glucagon and high glucose requirement. Mutation screening of *ABCC8* and *KCNJ11* was performed by HRM and DNA sequencing, MLPA and chr.. 11 LOH analysis in pancreatic tissue samples.
Results: Clinical characteristics and mutation screening results are summarized in the table below.
Nine different heterozygous *ABCC8* mutations (three novel, in bold) were detected in 9/11 (81.8%) patients: 3 missense, 2 nonsense, 2 frameshift, 1 in-frame duplication and 1 splicing mutation. 18F-DOPA PET detected focal forms in 4 patients. Three of them, unresponsive to diazoxide treatment, presented a paternally inherited *ABCC8* mutation and somatic loss of the maternal imprinted 11p15 region, whereas the fourth one, with a *de novo ABCC8* mutation, showed a partial diazoxide response (Table). Two patients presented with diffuse forms and had a partial response to diazoxide.
Conclusions: CHI clinical phenotype associated with loss of function mutations in *ABCC8* is highly heterogeneous, including both focal and diffuse forms as well as a variable sensitivity to diazoxide treatment.

CASE NR.	Birth weight (Percentile)	Age at diagnosis	Clinical symptoms	Initial management	Diazoxide sensitivity	PET results	Surgery	*ABCC8* mutation	Current treatment
1	P98	1st day of life	Tremor, lethargy	Diazoxide, HCTZ, octreotide	No	Focal	Focal pancreatectomy	p.Arg1250X (paternally inherited) & somatic loss of maternal allele	None
2	P73	5th month of life	Convulsions	Diazoxide, HCTZ, octreotide	Yes	NA	NA	**p.Ile1409Phe** (paternally inherited)	Diazoxide
3	P79	1st day of life	Convulsions	Diazoxide	Partial	Diffuse	NA	**p.Ser1018Leu** (maternally inherited)	Diazoxide
4	P59	5th month of life	Convulsions	Diazoxide, HCTZ, octreotide	Partial	Diffuse	Partial pancreatectomy	c.1177-56G>A (paternally inherited) predicted to affect splicing	Diazoxide recently suspended
5	P99	1st month of life	Convulsions	Diazoxide, HCTZ	No	Focal	Focal pancreatectomy	p.Leu503Pro (paternally inherited) & somatic loss of maternal allele	None
6	P62	1st day of life	Cyanosis, hypoactivity	Diazoxide, HCTZ, octreotide, Hydrocortisone	No	Focal	Focal pancreatectomy	p.Ala572_Leu582dup (paternally inherited) & somatic loss of maternal allele	None
7	P89	2nd month of life	Hypoactivity, convulsions	Diazoxide, HCTZ, Hydrocortisone	No	Bifocal	70% pancreatectomy	p.Arg836X (*de novo)*	None
8	P73	12 h of life	Cyanosis, hypotonia	Diazoxide	No	NA	90% pancreatectomy	p.Asp1192MetfsX16 (paternally inherited)	None
9	P40	1st day of life	Hypotonia, convulsions	Diazoxide, HCTZ, octreotide	Partial	NA	95% pancreatectomy	**p.Val1150LeufsX43** (unknown inheritance)	Diazoxide recently suspended, (light glucose intolerance)

[Patients clinical & molecular characteristics]

P1-d3-436 Glucose Metabolism 3

Long-term follow-up of individuals diagnosed with type 1 diabetes mellitus during childhood

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Background: Previous longitudinal studies have prospectively studied large numbers of patients diagnosed with Type 1 diabetes mellitus (T1DM) during childhood.
Objective: To outline the clinical course of T1DM in terms of glycaemic control, attendance rates, major microvascular complications and mortality for a cohort of patients diagnosed with T1DM in childhood who have transitioned from The Royal Children's Hospital, Melbourne (RCH) to Royal Melbourne Hospital (RMH) April1992-June 2012. This group accounts for 40% of the RCH clinic population.
Population and/or methods: Using Biogrid Australia© individuals common to both the RCH and RMH clinical databases were identified. Serial HbA1c results, attendance rates and the occurrence of major microvascular complications were noted where complete. Data for the entire cohort with subdivisions based on era of T1DM diagnosis were extracted.
Results: A total of 524 individuals were identified, diagnosed with T1DM 1975 - 2010. Demographics, major complications and glycaemic data are shown in Table 1. Clinic interval data between last RCH and first RMH appointments were available for 428 individuals; range 0.03-19.3 years; 46.49% had interval < =6 months, 42.52% had an interval of >1 year and 29.67% had an interval of >2years.
Conclusions: This cohort diagnosed with T1DM in childhood was managed based on the 'ideal' model of transition, from one multidisciplinary centre to another. The high rate of clinic interval >2 years reflects our previous data which demonstrated a 30% drop out rate after transition but further inference is limited.

	1975-1989	1990-1999	2000-2010	Total
n	117	183	224	524
Age at diagnosis (years)	5.6±3.8	7.4±3.7	11.6±2.6	8.2±4.1
Deaths (n)	1	1	0	2
Proliferative Retinopathy (n)	4	1	0	5
Serum creatinine >141 µmol/l	7	3	3	13
Amputation	0	2	0	2
Overall HbA1c (%,mean±sdev)	8.2±2.3	8.2±2.9	8.4±2.5	8.2±2.7

[Demographics, complications and HbA1c over time]

P1-d3-437 Glucose Metabolism 3

A mathematical model to predict HbA1c levels from mean blood glucose in young type 1 diabetic patients

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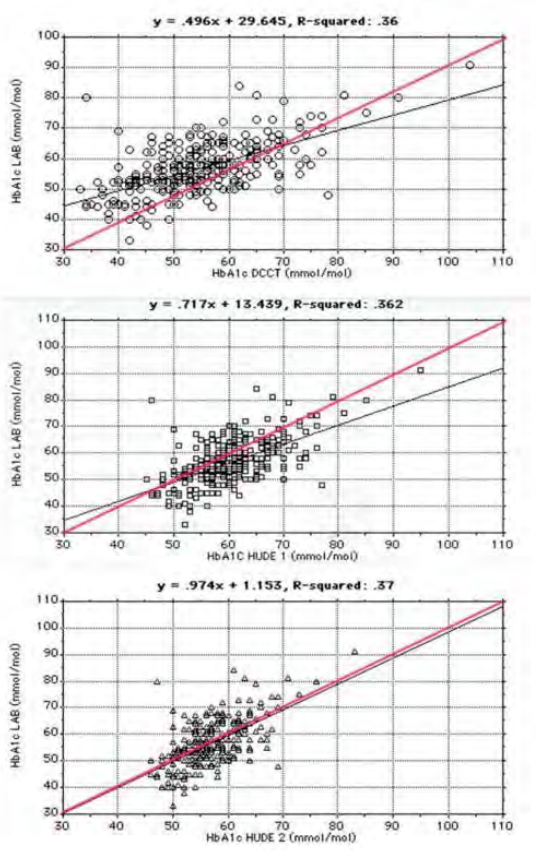
Background: The results of the Diabetes Control and Complications Trial (DCCT) established the relationship between HbA1c levels and risks for diabetic complications. Analysis of mean glucose (MG) profiles (premeal, postmeal, bedtime) and HbA_{1c} in the DCCT conducted to define a linear regression model with this equation: HbA_{1c}(%)=1.62+0.036xMG (p< 0.0001). In a previous study, we calculated another equation (HUDE1) predicting HbA1c from MG: HbA_{1c}(%)=3.83 +0.024xMG (p< 0.0001). However, there was a bias, i.e. some patients were enrolled more than one time in the study.
Objective: To define the relationship between preprandial MG and HbA_{1c} in a large cohort of young type1 diabetic patients enrolled only once.
Patients and methods: The study included 294 type1 diabetic patients with a median age of 14.7yr (10.1-21.7) and with a duration of diabetes of 6.2yr (2.7-13). The median number of preprandial blood glucose measurements, plus at bedtime, was 4.2 (3.9-4.7). Home blood glucose measurements, between 2 visits (about 2 months), have been downloaded from the meters. HbA1c was determined with the HPLC system. A statistical model was developed to predict HbA1c from MG.
Results: The MG (±1 SD) was 158±27 mg/dl and the mean HbA_{1c} (±1 DS) was 7.4 (=57 mmol/mol) ±0.9% (median: 7.2). Predicted HbA1c was calculated from the equation (HUDE 2): HbA1c (%)= 4.52 +0.18xMG (p< 0.0001). The figure 1 shows the simple regression lines between MG and HbA_{1C} (mmol/mol) in the 3 studies.



[Figure 1]

Conclusion: These data clearly show that the HUDE2 equation defines the best relationship between MG and HbA_{1c} and provides a good information to predict HbA_{1c} levels from blood glucose meters downloads.

P1-d3-438 Glucose Metabolism 3

Obesity and diabetes in youth: distinguishing characteristics at diagnosis and follow-up between islet cell antibody positive vs. negative patients

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Background: The clinical diagnosis of type 2 diabetes (T2D) in youth is largely driven by the presence of obesity. With increasing rates of obesity in patients with type 1 diabetes (T1D) the distinction between T2D and obese youth with autoimmune T1D has become difficult. In fact, 10-75 % of obese youth with clinically-diagnosed T2D (CDx-T2D) have evidence of islet cell autoimmunity.
Objective and hypotheses: To evaluate for distinguishing features of antibody positive (Ab+) vs. negative (Ab-) youth with CDx-T2D at diagnosis and at their most recent clinic visit.
Methods: Medical records of 151 patients seen at our institution from

January 2003 through July 2012 with CDx-T2D were reviewed. Diagnosis of T2D was based on the ADA diagnostic criteria. GAD-65 and IA-2 antibodies were measured by the NIDDK harmonization assay and Ab+ was defined as having at least one positive.
Results: The Ab- vs Ab+ group had more females (69% vs. 41%), African Americans (39% vs. 16%), acanthosis nigricans (78% vs. 51%) and lower DKA rates at diagnosis (6.2% vs. 24%).

At Diagnosis				At Follow up			
	Ab+ (n=73)	Ab- (n=78)	p value		Ab+ (n=73)	Ab- (n=78)	p value
Age (yrs)	12.8 ± 2.5	13.9±2.4	0.006	DM duration (yrs)	2.5	2.2	NS
BMI z-score	1.9 ±0.5	2.4±0.3	<0.001	BMI z-score	1.7 ±0.6	2.2 ±0.5	0.006
HgbA1c (%)	10.3 ±2.4	10.2 ±2.8	NS	HgbA1c (%)	7.8 ±2.1	7.6 ±2.4	NS
SBP (mmHg)	126 ±16	132 ±17	NS	SBP (mmHg)	118 ±10	124 ±13	0.004
Cholesterol (mg/dl)	153 ± 45	177 ± 43	0.003	On Insulin	83.8 %	55.1 %	<0.001
Triglycerides (mg/dl)	115 ± 83	181 ± 146	0.027	On Metformin	20.6 %	84.6 %	<0.001
C-peptide (ng/ml)	1.6 ±1.3	4.2±3.5	<0.001	± SD, SBP: systolic blood pressure			

[Results table]

Conclusions: At diagnosis, Ab- patients were older and heavier, with more clinical and biochemical evidence of insulin resistance and metabolic syndrome, and had higher C-peptide compared to Ab+ youth but no difference in HbA1c. At follow up, these differences persisted, with insulin used more often in Ab+ patients and metformin therapy used more often in Ab- youth. The overlap in clinical presentation may justify the need for autoantibody testing to help guide treatment plans.

P1-d3-439 Glucose Metabolism 3

Characterising the role and regulation of dipeptidyl peptidase-4 in congenital hyperinsulinism

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Background: Congenital hyperinsulinism (CHI) is characterised by persistent hypoglycaemia due to unregulated secretion of insulin from the pancreatic β-cells. The incretin hormones: glucagon like peptide-1 (GLP-1), glucose-dependent inhibitory peptide (GIP) and the gut hormone peptide tyrosine tyrosine (PYY) are all known to have a role in glucose homeostasis. However, the role of these hormones is not known in patients with hyperinsulinaemic hypoglycaemia. Preliminary data suggested that the expression of dipeptidyl peptidase-4, the enzyme that regulates these gut hormones was significantly increased in patients with diffuse CHI with a trend for a reduction in *PYY* mRNA.
Objective: To assessed the localisation of DPP-4 and PYY in different islet-cells as well as confirm the cells that were proliferating in CHI.
Patients and methods: Using immunohistochemistry, DPP-4 & PYY was localised in 8 healthy control tissues as well as in 8 diffuse CHI pancreata. In addition, five diffuse CHI patients underwent a controlled hypoglycaemia screen (reducing iv glucose with no feeds) and blood was collected at euglycaemia and at hypoglycaemia. Plasma glucose was measured using YSI and insulin by RIA. Total and active GLP-1, total GIP were measured using ELISA and total and active PYY were measured using RIA.
Results: We found that in a normal healthy pancreas, islet PYY is expressed in α-cells, whereas, DPP-4 was found in α, β and δ-cells. Diseased pancreas confirmed that β-cells were the only cells proliferating and showed co-expression of insulin and DPP-4. In addition, we evaluated if changes in circulating GLP-1, GIP and PYY in CHI patients at euglycaemia and hypoglycaemia could indicate a role for these gut hormones and their enzyme. Plasma insulin levels remained detectable at hypoglycaemia. Plasma glucose, GLP-1and PYY all decreased at hypoglycaemia with a trend for a fall in GIP (*p=0.07*) from euglycaemia.
Conclusion: In conclusion, patients with CHI provide a unique model to understand the physiological interactions of islet DPP-4 and insulin as an alternative model to the traditionally used diabetes model. This knowledge will provide new insights into the interactions between insulin and hormones that DPP-4 regulates prior to the occurrence of insulin resistance.

P1-d3-440 Glucose Metabolism 3

A randomised controlled trial of a psychological intervention to improve metabolic control in children with type 1 diabetes

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Background: Psychiatric morbidity is increased in patients with type 1 diabetes and has negative effects on disease management, increasing risk for long term complications.
Objective: We conducted an RCT (Clinical Trial: ACTRN12609000710224) of a standardised, evidence-based psychological intervention.
Methods: Children (N=83, 4-12 yrs) and their mothers recruited from Royal Children's Hospital and randomly allocated to intervention and control groups. Mothers completed pre-intervention measures of child behaviour, psychological well-being, parenting skills and conflict. Measures were repeated at 3 and 12 months. HbA1c levels were measured at 3,12 & 24 months post intervention. Intervention mothers completed the Triple P Program which teaches core parenting strategies.
Results: Behaviour problems, maternal symptoms and parenting conflict were lower and parenting skills were higher in the Triple P group at 3 months, but not at 12 months. Groups did not differ on diabetes-related conflict or metabolic control (HbA1c levels) at any time point - Table 1.

	3 month post intervention			12 month post intervention			2 years post intervention		
	Triple P (N=42) M (SD)	Control (N=41) M (SD)	p level	Triple P (N=42) M (SD)	Control (N=41) M (SD)	p level	Triple P (N=42) M (SD)	Control (N=41) M (SD)	p level
Glycemic control (HbA1c)	7.94 (0.85)	7.71 (0.85)	0.29	7.90 (1.04)	7.59 (0.95)	0.19	7.90 (0.88)	7.86 (0.97)	0.90
Externalising problems	46.24 (7.33)	47.93 (8.40)	0.02	45.78 (6.07)	45.32 (6.94)	0.70			
Internalising problems	47.31 (8.28)	51.50 (11.29)	<0.01	48.16 (10.55)	50.16 (15.4)	0.20			
Parent depression	1.18 (2.21)	4.57 (6.14)	0.01	2.13 (3.12)	2.96 (3.38)	0.43			
Parent stress	2.89 (3.73)	6.83 (7.74)	<0.01	4.23 (3.84)	5.48 (3.87)	0.09			
Diabetes family conflict	21.38 (2.43)	22.81 (3.34)	0.051	23.44 (5.24)	22.56 (3.29)	0.96			
Parenting conflict	2.30 (2.61)	4.52 (4.92)	<0.01	3.16 (3.35)	3.08 (3.71)	0.84			
Parenting satisfaction	39.83 (6.32)	37.13 (6.75)	<0.01	39.38 (6.34)	37.60 (6.87)	0.13			

[Table 1 Child, parent and family outcomes]

Conclusions: Child behaviour, maternal wellbeing and parenting skills improved initially in the treated group but there was no long-term benefit from Triple P. There was no impact on metabolic control. Findings highlight the importance of longer-term follow-up in any evaluation of the efficacy of psychological intervention aimed at reducing psychiatric morbidity and improving metabolic control in children with type 1 diabetes.

P1-d3-441 Glucose Metabolism 3

The efficacy of using the internet-based CareLink® therapy management system for diabetes in patients with type 1 diabetes (T1D)

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Background: CareLink® for Diabetes is a Web-based therapy management system designed to simplify data collection.
Objective: To assess the efficacy of the CareLink® system on metabolic control, patient's satisfaction (PS) and quality of life (QOL).
Methods: In a randomized-controlled trial, 70 patients with T1D (mean diabetes duration 6.4 ± 4.7 years), treated with CSII ≥3 months, mean age 14.0±5.3 years, mean HbA1c 8.68±0.68% were randomized to: an intervention group (n =36) and a control group (n=34). During a 4-month period, in the intervention group usage of CareLink® was assisted by the diabetes team through at least monthly internet contact, in which patients submitted their pump and glucose levels data; whereas subjects in the control group were instructed to submit monthly blood glucose levels via fax/email and were instructed for treatment adjustments by the same team. In the next 4 months patients from both groups were instructed to use the system at home. HbA1c levels, PS and QOL questionnaires were assessed at baseline, at 4 and 8 months.
Results: After 4 months, HbA1c levels decreased compared to baseline (intervention: 8.75±0.84% to 8.45±0.90%, p=0.013; control: 8.65±0.57% to 8.37±0.73%, p=0.054). Patients in both groups that submitted data< 3 times during each 4-month segment were classified as non-compliant. Only in the intervention group the difference in HbA1c levels after 4 months between compliant and non-compliant patients was significant (8.17± 0.81% vs. 8.99±0.85%, p=0.017), with a significant decrease in HbA1c in the compliant group (p=0.006). After 8 months, in the control group compliant patients who used the Carelink® had a significant decrease in HbA1c level compared with baseline (p=0.018).
No significant changes were found in PS or QOL scores during follow-up in both groups.
Conclusions: Use of the CareLink® system was associated with a significant improved glycemic control only in compliant patients, without a change in PS or QOL.

P1-d3-442 Glucose Metabolism 3

Cognitive and neuroanatomical differences in young children with type 1 diabetes (T1D) and association with dysglycaemia: the diabetes research in children network (DirecNet) experience

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Background: Studies suggest there are detectable differences in gray and white matter structure in adolescents and adults with T1D, and severe hypoglycemia is associated with poorer cognitive outcomes.
Objective: To characterize neuroanatomical and neuropsychological differences in very young children with T1D compared to non diabetic controls.
Methods: 142 children with T1D (mean (SD) age: 7.0 ±1.7 yrs (4-9), 76 males, median diabetes duration 2.5yrs) and 68 non diabetic controls (7.0 ±1.8 yrs, 35 males) had unsedated brain magnetic resonance imaging and age-appropriate neurocognitive testing and HbA1C. The T1D group wore a continuous glucose monitor (CGM) for ~6d. Voxel based morphometry and diffusion tensor imaging analysis and correlations with glycemic indices were performed.
Results: Relative to controls, the T1D group displayed decreased gray matter volume (GMV) in occipital and cerebellar regions (p< 0.001) and increased GMV in left temporal and prefrontal cortices (p=0.002), differences correlated with greater hyperglycemia. Severe hypoglycemia correlated with increased GMV in occipital temporal regions and decreased GMV in medial temporal lobes. Children with T1D had reduced axial diffusivity in widespread brain regions compared with controls. HbA1c was negatively correlated with fractional anisotropy and positively with radial diffusivity values in multiple brain regions, changes correlating with CGM measures of hyperglycemia and glucose variability, not hypoglycemia. Covarying for age, gender, and parental IQ, children with T1D had lower IQ scores (p=.02) and executive functions (p=.02), and more depressive and somatic symptoms by parental rating (p< 0.001).
Conclusions: Differences in neuroanatomy, cognition and mood are detectable in very young children with T1D within 2 years of disease onset. Ongoing longitudinal 18 months follow up analysis of this cohort will further describe the neurodevelopmental trajectory of very young children with T1D.

P1-d3-443 Glucose Metabolism 3

Higher albumin creatinine ratio is associated with cardiac autonomic dysfunction in adolescents with type 1 diabetes

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Background: Adults with diabetic renal disease often have coexisting autonomic neuropathy and have higher risk for cardiac disease.
Hypothesis: Autonomic dysfunction occurs early in the course of abnormal albumin excretion in adolescents with type 1 diabetes (T1D), which may drive or coincide with early renal disease.
Objective: To determine whether adolescents at risk of microalbuminuria, indicated by higher urine albumin:creatinine ratios (ACR), have an adverse autonomic profile, measured by heart rate variability (HRV).
Methods: Adolescents with T1D duration >1 year (n=399, 49% female, aged 10-16 years) were recruited as part of a multicentre nephropathy screening study for eligibility to AdDIT. Standardised ACR were calculated from 6 early morning urine collections (adjusted for age, gender and diabetes duration) and stratified by tertiles. HRV parameters were derived from a 10-minute continuous ECG recording using LabChart Pro; including baseline HR, measures of overall HRV (SDNN, RMSSD and triangular index) and measures of sympathetic and parasympathetic components (LF, HF and LF:HF ratio). Contemporary age-matched controls (n=55) were assessed using the same equipment.
Results: Comparing the upper tertile ACR (n=202) with middle and lower tertiles (n=197), adolescents were younger (mean 14.1 vs 14.6 years, $p< 0.01$) with shorter diabetes duration (6.2 vs 8.2 years, $p< 0.01$), but there was no difference in HbA1c (group mean 8.4%, 68mmol/mol) or cholesterol levels (4.5mmol/L). They had higher HR (median 74 vs 72bpm, $p=0.03$), lower HRV parameters (SDNN 63 vs 70, $p=0.03$; RMSSD 53 vs 63, $p=0.04$; LF power 936 vs 1275, $p=0.03$; triangular index 14.7 vs 15.9, $p=0.04$). Compared with age-matched controls, adolescents with diabetes had lower HRV even adjusting for their higher BMI.
Conclusions: Cardiac autonomic dysfunction, indicated by higher HR and lower HRV, is found in the earliest stages of diabetic renal dysfunction, implying higher risk for cardiac disease.

P1-d3-444 Glucose Metabolism 3

First child with glucagonoma: multiple endocrine neoplasia type 1 presenting with hyperinsulinaemic hypoglycaemia and simultaneous glucagonoma and insulinoma, identified by [68Ga]DOTATATE PET/CT and [111] In-Exendin-3 SPECT, respectively

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Background: Multiple Endocrine Neoplasia type 1 (MEN1) rarely presents with insulinoma. Imaging of insulinomas remains a challenge.
Objective and hypotheses: To diagnose and treat a 14-y-old girl with hyperinsulinemic hypoglycemia (HH).
Methods: DNA-sequencing of *MEN1*, [^{18}F]DOPA PET/CT, [68Ga] DOTATATE PET/CT and [111] In-Exendin-3 SPECT scan.
Results: Biochemical evaluation showed severe HH, p-glucose 2.7mM, insulin 342 (18-173)pM, C-peptide 1613 (370-1470)pM, proinsulin 75 (2-23) pM, treated by iv. glucose and glucagon. Other hormones were normal. A heterozygous mutation in *MEN1*, p.Ala464Glyfs*65, was found. Endoscopic ultrasound and MRI revealed no tumor. A focus in the head of the pancreas was seen by [68Ga]DOTATATE PET/CT and resected, but afterwards the hypoglycemia surprisingly became more profound. Pre-surgery fasting serum glucagon revealed to be 100-fold elevated (no glucagon infusion) and post-surgery histological staining showed glucagonoma. By [^{18}F]DOPA PET/CT, an indistinct area in the head of the pancreas had moderately increased uptake. A modified Roux-en-Y was performed, after which a slow relapse of HH to former levels occurred. Through international collaboration, a [111] In-Exendin-3 SPECT scan (targeting the Glucagon-Like Peptide 1 receptor) finally showed pathological uptake close to Papilla Vateri.
The patient's father also had the *MEN1* mutation and had undiagnosed Zollinger-Ellinson Syndrome, hyperparathyroidism, hyperprolactinemia, and highly increased chromatogranin A, but no hyperinsulinemia or hyperglucagonemia.
Conclusions: This is the first report of a child with a glucagonoma. The glucagonoma was masked by a simultaneous insulinoma and clinical HH due to MEN1. [68Ga]DOTATATE PET/CT detected the glucagonoma, but not the insulinoma. [111]In-Exendin-3 is a promising tool for the identification of otherwise undetectable insulinomas. Family evaluation of insulinoma patients may detect MEN1 in elder family members with euglycemia.

P1-d3-445 Glucose Metabolism 3

Adverse inflammatory profile during luteal phase (LP) in adolescents with type 1 diabetes (T1D)

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Background: Chronic complications and mortality rate for cardiovascular diseases are higher in premenopausal women with T1D than healthy males of similar age.
Objective and hypotheses: We hypothesize that a detrimental inflammatory profile during LP may represent a unique phenomenon present in women.

Our aims are: 1.-To study ultrasensitive C-reactive protein (usCRP) levels during follicular phase (FP) and LP in adolescents with T1D. 2.-To evaluate the prevalence of elevated usCRP (>3ng/ml), a marker of cardiovascular risk.
Methods: We evaluated 40 adolescents with T1D and 33 healthy adolescents (C) during FP and LP. usCRP was measured with usELISA kit. Ovulation was determined by a progesterone level >4ng/ml in day 21-23. Non-parametric statistics were used.
Results: T1D and C girls showed a similar proportion of ovulatory cycles (35.0% T1D and 30.3% C, P=0.8). T1D adolescents showed higher levels of usCRP compared to C group in FP and LP in ovulatory and anovulatory cycles (both P< 0.05). An elevation of usCRP levels in LP compared with FP was observed in ovulatory and anovulatory T1D girls (Wilcoxon paired test, P=0.001), and in anovulatory C girls (P=0.0001). The prevalence of usCRP >3 ng/ml was similar in FP, but higher in T1D than C girls in LP (90% vs. 28.6%, P< 0.05). Follicular usCRP was associated with estrone levels in T1D girls.
Conclusions: Elevated usCRP levels are observed in T1D girls especially during LP. An elevation of this marker in LP occurs in T1D adolescents and anovulatory C adolescents. T1D girls exhibit a higher prevalence of elevated usCRP in luteal phase of the menstrual cycle compared to healthy girls. Estrone levels are associated with elevated follicular usCRP in T1D. We postulate that increased inflammatory markers in LP may be involved in the pathogenesis of an adverse risk profile for cardiovascular complications (Fondecyt 1100123).

P1-d1-446 Glucose Metabolism 4

Pesticides immunotoxicity in diabetic Egyptian children during first presentation

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Background: Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder that could be triggered by environmental pollutants in genetically susceptible individuals.
Objective and hypotheses: The present study aimed to assess the immune response of different lymphocyte subpopulations in a group of diabetic children in relation to pesticides with highest Odds ratios (lindane and malathion).
Methods: Seventy five Diabetic Egyptian children during first month of clinical presentation; their ages ranged from 1.2 to 10 years were studied. The control group comprised 35 age and sex matched healthy children. Seven ml whole peripheral blood sample was collected from each child and was divided as follows: 5 ml blood was taken for toxicological analysis of pesticides residues using Gas Chromatography equipped with Ni^{63} Electron Capture Detector. The remaining 2 ml blood sample was collected in EDTA tubes and used immediately for testing immunological markers by using flowcytometry.
Results: Significant correlation as regards the expression of CD4 %, HLADR % and CD4/CD8 ratio in relation to lindane. While malathion (an organophosphate compound), shows a significant correlation with CD4 %, CD20 %, CD16 % and HLDAR % lymphocyte subsets in the diabetic group compared to healthy subjects.
Conclusions: Pesticides might play a role concerning the increased incidence of T1DM in children.

P1-d1-447 Glucose Metabolism 4

Abstract has been withdrawn

P1-d1-448 Glucose Metabolism 4

Impact of protein and fat rich meals on glucose levels. A study in adolescent patients with type 1 diabetes (T1D)

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Background: The effect of carbohydrates (CH) on blood glucose levels is unquestioned. Some studies also presume that protein and fat influences blood glucose. Until now the magnitude of these influences is unclear.
Objective: We aimed to investigate the influence of a fat and protein rich meal on glucose levels in adolescent patients with T1D.
Patients and methods: Fifteen adolescent (2 female) patients (mean (SD) age 16.8 (2.9) yrs, HbA1c 6.9 (0.6) %, insulin dose 0.9 (0.3) IU/kg/d) with T1D were investigated. On two consecutive days they received a standard (SM) (fat 19 g = 30 kcal%, protein 28 g = 20 kcal%, CH 70 g = 50 kcal%) and a fat protein rich (FPM) evening meal (fat 52 g = 40 kcal%, protein 110 g = 40 kcal%, CH 70 g = 20 kcal%). Insulin for CH was injected with the individual carbohydrate bolus. Glucose was measured continuously with the Enlite Sensors and the Guardian (Medtronic) over night during the following 12 hours after the meal.
Results: Glucose area under the curve (AUC) for SM was 1400 (580) mg/dl/12h and for FPM 1967 (394) mg/dl/12h (p< 0.05). There was a significant difference in the AUC between 4 and 12 hours after the meal. Maximal AUC difference was 6 hours after the meal. The difference in morning glucose was 62 (50) mg/dl (p< 0.05). For SM 31% of glucose levels were < 80 mg/dl and 24% >150 mg/dl, for FPM it was 3% and 48%.
Conclusions: In adolescent patients with T1D glucose levels are significantly higher when eating a fat and protein rich meal. This effect is detectable untill 12 h after the meal. Subsequent studies have to prove how this effect can be reduced by additional insulin administration.

P1-d1-449 Glucose Metabolism 4

Improvement of diabetes self-management skills in children and adolescents with type 1 diabetes mellitus

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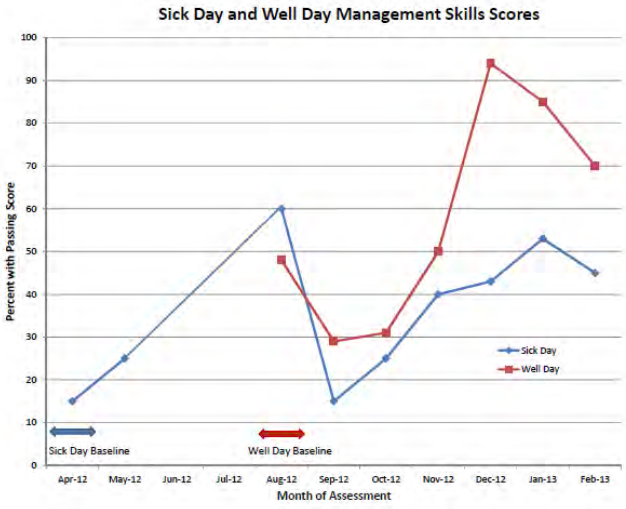
Background: Patients with Type 1 diabetes mellitus (T1DM) require comprehensive self-management skills to achieve optimal diabetes care and control. Most diabetes programs have comprehensive diabetes education practices in place, yet no standardized objective assessment tools exists to evaluate the level of learning.
Objective and hypotheses: To develop objective assessment tools to evaluate the level of proficiency for well-day, sick-day, and pattern recognition self-management skills in patients with T1DM and to utilize this information to improve our diabetes education program.
Methods: Three vignette-based assessment questionnaires were developed to evaluate diabetes skills in regards to: well-day self-management, sick-day self-management, and pattern recognition of blood glucose levels. Each questionnaire was administered to 20 T1DM patients at random every month. The assessment scores were tracked monthly on run charts. Interventions to improve clinic diabetes education were made based on identified deficiencies.
Results: Well-day and sick day management skills score improved from 47% to 70% and 15% to 45% respectively.



[Sick Day and Well Day Management Skills Scores]

Conclusions: This quality improvement initiative demonstrated to us that the efficacy of our diabetes education was less than anticipated. We realized that objective measures are essential to evaluate the initial level of learning as well as subsequent improvement. New evaluation measures may be developed if none exist. Our work clearly demonstrates the need for a paradigm shift in the medical provider-patient interaction of meeting self-management educational needs of patients with chronic illnesses such as diabetes mellitus.

P1-d1-450 Glucose Metabolism 4

In children with type 1 diabetes mellitus, anti-tissue transglutaminase antibody levels may spontaneously normalise despite a gluten normal intake

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Background: The prevalence of celiac disease (CD) among type 1 diabetes mellitus patients (T1DM) is higher than in the general population. Serological screening is necessary, because anti TTG-IgA levels may spontaneously normalize.
Objective and hypotheses: We aimed to investigate the prevalence and extent of spontaneous normalization of TTG-IgA antibody levels in patients with T1DM and to identify possible predictive factors of seronegativization of celiac serology.
Population and/or methods: The study group was a cohort of 446 children (M: 246; F 200), affected by T1DM and diagnosed between 2001-2013, who were prospectively screened for CD. Out of these, 381 (85,5%) resulted persistently negative for CD serology (T1DM), 38 (8,5%) were diagnosed with CD (T1DM-CD) and 27 (6%) had spontaneous decline/negativization of CD serology (T1DM-CDneg). Clinical and serological data were prospectively recorded to identify predictive factors for celiac serology negativization.
Results: During follow-up (mean±SD: 6.7±3.1y), the titer of serological tests, in the TTG-IgA positive group, spontaneously decreased in 41% while on a gluten- containing diet. In these group of patients, serology showed a progressive reduction with normalization in 18 (66,7%); 3 (11.1%) became subsequently positive. The age at first anti-TTGA positivity was lower in T1DM-CD compared to T1DM-CDneg (7.03±3.48 vs. 11.25±5.3; p< 0,0005). Serum anti-TTG-IgA levels were higher in T1DM-CD as compared to T1DM-CDneg children at first time of TTG-A positivity (p< 0,0001). Median time to normalization for anti-TTG was 0,86y(range: 0.10 - 4.39).
Precise conclusions: In T1DM patients with positive serum anti-TTG levels, the celiac serology may spontaneously decrease/normalize, on a gluten normal intake. An accurate follow-up and a "wait and see" policy, may help avoiding unnecessary invasive diagnostic procedures and reducing psychological burdens that a gluten-free diet would add, further affecting quality of life.

P1-d1-451 Glucose Metabolism 4

Both homoarginine and asymmetric dimethylarginine are decreased in children and adolescents with type 1 diabetes, and are unaffected by statin treatment

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Background: Homoarginine (HoArg) and asymmetric dimethylarginine (ADMA) are associated with nitric oxide synthesis, endothelial function, and cardiovascular disease.
Objective and hypotheses: The role of HoArg and ADMA regarding these processes in pediatric type 1 diabetes (T1D) is largely unknown and needs further evaluation.
Methods: Arginine (Arg), HoArg, ADMA, and carotid intima-media thickness (cIMT) were measured at baseline and two years after treatment with 10 mg Sortis (atorvastatin, ATV, n = 18) or placebo (n = 10) within a double-blind pilot study in children and adolescents with T1D. Data from 41 age- and sex-matched healthy non-diabetic peers (NDPs) were used for comparison.
Results: At baseline, both HoArg and ADMA were significantly lower ($P <$ 0.001) in children with T1D compared to NDPs. After two years, both HoArg and ADMA showed no significant difference between diabetic patients receiving either ATV or placebo. In diabetic children, there were inverse correlations between HoArg and HbA1c ($P < 0.001$) and between ADMA and systolic blood pressure (p = 0.005) and pulse pressure ($P = 0.003$).
Conclusions: Reduced plasma levels of HoArg and ADMA in diabetic children compared to NDPs suggest that the two parameters may have the potential to serve as early markers of developing atherosclerotic vascular changes in pediatric T1D. This is supported by their associations with the generally accepted atherogenic risk factors hyperglycemia and blood pressure. The two-year ATV therapy did not have any significant influence on plasma concentrations of HoArg and ADMA.

P1-d1-452 Glucose Metabolism 4

Is insulin resistance more frequent in children born small for gestational age?

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Background: Rapid increase in weight during early childhood, "catch-up growth" phenomenon, in children born small for gestational age (SGA) has been strongly linked with insulin resistance (IR), which may be a risk factor for type 2 diabetes mellitus and cardiovascular disease.
Methods: A retrospective observational study was carried out on long-term metabolic complications in children born SGA, which were admitted to our hospital over a 5 year period from 2007 to 2011. 517 patients (mean age 12 years±0.6, aged between 6 - 18 years) were divided in two study groups, following the statistical processing of data sheets, as follows: 410 obese patients that were born appropriate for gestational age (AGA) (79.30%) and 107 obese

patients that were born SGA (29.69 %). Glucose and insulin levels of the patients were measured and the insulin resistance index (IR) was assessed by homeostasis model assessment (HOMA). A cut-off HOMA level of >2.5 in the prepubertal period and of >3.5 for adolescents was used to identify an insulin-resistance status.
Results: Insulin resistance was found in 20% of obese AGA children and 25.3% of obese SGA. Rate of insulin resistance in patients born SGA was greater compared to obese children born AGA and had a significant statistical difference (P = 0.03, mean 2.95 AGA versus 3.73 SGA group and SD 1.7 versus 2.6).
Conclusions: Increased prevalence of IR patients born SGA compared to AGA indicates that being born SGA appears to be an additional risk factor in the development of IR. IR met in a high percentage among obese patients born SGA allows us to affirm that the cardiovascular risk in these patients as well as the risk of developing type 2 diabetes is higher. Monitoring, periodic evaluation and appropriate dietary therapy in the case of obese children born SGA is crucial in preventing early onset of cardiovascular disease.

P1-d1-453 Glucose Metabolism 4

Profile and outcome of diabetic ketoacidosis treated in a tertiary care referral centre in a developing country

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Background: International Society of Paediatric and Adolescent Diabetes (ISPAD) guidelines improve outcome in paediatric Diabetic ketoacidosis (DKA).
Objective and hypotheses: To describe the clinical profile and outcome of DKA treated in a tertiary care paediatric referral hospital in a developing country managed using the ISPAD guidelines.
Methods: Retrospective review of case records of children managed in the paediatric intensive care unit from January 2010 to December 2012.
Results: Records of 21 children (70%) with Type 1 diabetes who presented in diabetic keto acidosis were reviewed. 90.4% were first episode DKA. 21 children (mean age 6.8 ± 4.5 years, 10 males) were treated using the ISPAD guidelines in the study period. The presenting symptom was either polydipsia (61.9%), polyuria (66.7%), polyphagia (23.8%) or abdominal pain (42.9%). In our series, the mean potassium, sodium, pH and serum bicarbonate was 4.1±0.6, 133.3±5.3, 7.16±0.1 and 11.6±6.8 respectively. The severity of DKA was classified as mild, moderate and severe in 55.5%, 11.1% and 33.3% respectively The mean duration (in hours) of intravenous fluids, intravenous insulin and hospital stay was 24.7 ± 17.3, 24.5±14.7 and 138.4±53.8 respectively. The duration of intravenous fluids, intravenous insulin, occurrence of cerebral edema and duration of hospital stay were similar in children < 5years and ≥ 5years (p-value >0.05). There was significant co-relation between duration of IV fluids and pH (r=-0.76, p-value < 0.05) & amount of IV fluids(per kilogram) and serum bicarbonate (r = -0.82, p-value < 0.05). Two children had cerebral edema during course of therapy, one treated with 20% mannitol, other with 3% saline infusion for 16 hours. One child who was eligible for serum bicarbonate therapy as per the ISPAD criteria received it. 0% mortality was noted in our series.
Conclusions: The ISPAD guidelines are indeed useful in management of pediatric DKA in developing countries.

P1-d1-454 Glucose Metabolism 4

A novel *GATA6* mutation leading to congenital heart defects and permanent neonatal diabetes: a case report

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Background: Permanent neonatal diabetes mellitus is a rare condition mostly due to heterozygous mutations in the *KCNJ11*, *ABCC8*, and *INS* genes. Neonatal diabetes due to pancreatic agenesis is extremely rare. Mutations in *PDX1*, *PTF1A*, *HNF1B*, *EIF2AK3*, *RFX6* and *GATA6* genes have been shown to result in pancreatic agenesis or hypoplasia.
Objective and hypotheses: To describe the clinical properties and genetical analysis results of a patient with permanent neonatal diabetes due to a novel GATA6 mutation.
Methods: In this report, we describe a 40 days old male diagnosed as permanent neonatal diabetes associated with atrial septal defect, pulmonary stenosis, patent ductus arteriosus.
Results: Besides permanent neonatal diabetes, the patient had transient idiopathic neonatal cholestasis and hypoglycemic episodes unrelated to insulin treatment, features which are rarely described in children with permanent neonatal diabetes mellitus. An echocardiography revealed secundum atrial septal defect (ASD), mild pulmonary stenosis (PS) and patent ductus arteriosus (PDA). Abdominal ultrasonography in the neonatal period revealed normal liver, gall bladder, bile ducts, and kidneys with a small (hypoplastic) pancreas. An abdominal MRI failed to identify any pancreatic tissue. A novel *de novo* heterozygous missense mutation (p.N466S) in the *GATA6* gene was detected in the patient who had no evidence of exocrine pancreas insufficiency.
Conclusions: We emphasize the importance of screening *GATA6* gene in PNDM patients with congenital cardiac defects even in the absence of exocrine pancreas manifestations and suggest that patients with PNDM due to *GATA6* mutations may also manifest idiopathic liver failure and cholestasis.

P1-d1-455 Glucose Metabolism 4

Medication induced diabetes during induction treatment for ALL, an early marker for future metabolic risk?

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Background: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. Medication induced diabetes (MID) is seen mostly during induction, due to the use of L-Asparaginase and glucocorticoids. Whether this common complication carries long term metabolic implications is unknown.
Objective and hypotheses: To assess whether MID during induction, in children with ALL, is a risk factor for developing future impaired glucose tolerance (IGT), diabetes or other components of the metabolic syndrome.
Methods: Survivors of pediatric ALL, ages 10 years and older were recruited. MID was defined as glucose level ≥ 200 mg/dl on 2 separate days during remission induction. Waist/height ratio ≥0.5 was considered as increased risk for central adiposity and insulin resistance as described in previous studies. Lipid profile and an oral glucose tolerance test (OGTT) were performed.
Results: 90 patients were recruited. Patients in the study group (n=30) were older than controls (n=60) (17.2 vs 14.9) (p< 0.05). The groups had similar sex distribution, BMI-SDS and Tanner staging. A waist/height ratio of ≥0.5 was seen in 60% and 31.7% of the study and control groups respectively (p-0.01). Increased frequency of IGT in the study group compared to the control group was seen (13.3% and 1% respectively) (p-0.07). We observed a trend towards higher proportion of patients with multiple features of metabolic syndrome in the study compared to control group (16.7% vs 5%) (p-0.09).
Conclusions: MID during induction may be an early marker for metabolic disturbances later in life. The higher rates of increased waist/height ratio, and

subjects with multiple metabolic syndrome features, may predict a metabolic risk in children with history of MID. Rates of IGT were four fold higher in the study group although not statistically significant. MID may be a 'red flag' indicating the need for ongoing metabolic screening and lifestyle modifications to prevent future metabolic disease.

P1-d2-456 Glucose Metabolism 5

A study on correlation between blood glucose fluctuations and activation of oxidative stress in type 1 diabetes children during the acute metabolic disturbance period

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Background: Studies have shown that complications in type 1 diabetes (T1DM) in children are caused by oxidative stress (OS). Lipid peroxidation is the main marker of OS and isoprostanes are reliable biomarkers of lipid peroxidation in type 2 diabetes (T2DM). There has been insufficient study of OS in T1DM children with hyperglycemia and glucose fluctuations.
Methods: We prospectively enrolled 23 newly diagnosed T1DM inpatients in our hospital from May 2010 to January 2011. They were treated with CSII and monitored by CGMS. Twenty-four hour urine samples were collected from these subjects and 23 age and sex matched healthy controls to measure concentration of 8-iso prostaglandin F2α (8-isoPGF2α). Samples taken from diabetic children were collected at days 8 to 10 after insulin treatment. Intraday glucose fluctuations were assessed by MAGE (mean amplitude of glucose excursions), LAGE (largest amplitude of glycemic excursions), SDBG (standard deviation of blood glucose) and NGE (number of glycemic excursions). The correlations between glucose parameters and index of oxidative stress were analyzed.
Results: Urine 8-isoPGF2α level in T1DM group was higher than control group (967.70±412.68 ng vs. 675.23±354.59 ng, p=0.019). The study reveals a correlation between the mean 24 h urinary excretion rate of free 8-isoPGF2α and MAGE (r=0.321, p=0.03). There is also significant correlation between LDL and the mean 24 h urinary excretion rate of free 8-isoPGF2α (r=0.419, p< 0.05). There was no significant correlation between the mean 24 h urinary excretion rate of free 8-isoPGF2α and blood pressure, HbA1c, fasting C-P or other lipid indexes.
Conclusions: There is a correlation between the mean 24 h urinary excretion rate of free 8-isoPGF2α, MAGE and LDL in children newly diagnosed with T1DM, which has already been reported in adults with T2DM but no positive reports in adults with T1DM.

P1-d2-457 Glucose Metabolism 5

Plasma insulin levels during an OGTT are positively correlated with height in obese pre-pubertal children and adolescents: implications for OGTT interpretation

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Background: There is a negative relationship between height and glucose half-life in the intestine.
Objective and hypotheses: To determine a possible correlation between subject's height and levels of plasma glucose and insulin during an OGTT in obese children and adolescents.
Methods: A total of 469 subjects were included; 44 obese pre-pubertal girls (age < 8 years, BMI 3.2 ± .1 SDS), 48 obese pre-pubertal boys (age < 9 years, BMI 3.0 ± .1 SDS), 228 obese adolescent girls (BMI 2.7 ± .0 SDS) and 169 obese adolescent boys (BMI 2.5 ± .0 SDS). OGTT (1.76 g glucose per kg, max. 75 g) was performed. Plasma samples were collected at 0', 30', 60' and 120'.
T-test and Person's correlation coefficient were used to determine differences and correlation between groups.
Results: Pre-pubertal and adolescent boys were taller than corresponding girls (131 ± 2 vs. 123 ± 2 and 164 ± 1 vs. 160 ± 1 cm respectively; P < 0.01). No differences were observed at any time point between prepubertal boys and girls in glucose or insulin, and between adolescent boys and girls in glucose levels. Adolescent girls, compared to boys, however had significantly higher insulin levels at 60' (107 ± 5 vs. 87 ± 5 mU/l) and 120' (96 ± 5 vs. 82 ± 5 mU/l). They also had significantly higher BMI-SDS.
Interestingly, in all subjects height positively correlated with plasma insulin levels at all OGTT time points and insulin sensitivity indexes derived from time 0' values (HOMA, QUICKI (negative correlation))(range r=0.488 to 0.170). An exception were adolescent girls where only a tendency toward positive correlation was determined at 30', 60' and 120'. No such correlation could be determined for glucose levels in any group.
Conclusions: Plasma insulin levels during OGTT are positively correlated with height in obese pre-pubertal children and adolescents, especially at time 0'. Subject's height should therefore be considered in the interpretation of an OGTT, especially in relation to plasma insulin levels.

P1-d2-458 Glucose Metabolism 5

Vitamin D deficiency and insulin resistance in Korean girls

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Background: Vitamin D is thought to be associated with cardiometabolic risk factors, and it may play a role in glucose metabolism. Vitamin D deficiency has been associated with an increased risk of diabetes in adults, but large population-based studies of the relationship between vitamin D deficiency and the risk of diabetes in children in Korea are rare.
Objective and hypotheses: The objective of this study is to investigate the association of vitamin D deficiency with insulin resistance and other metabolic risk factors in Korean children using a large population-based survey.
Methods: We assessed the data of 1,052 Korean children and adolescents aged 10-12 years obtained from the 2008-2010 Korea National Health and Nutrition Examination Surveys. We defined vitamin D deficiency as 25-hydroxyvitamin D < 20 ng/mL; and compared values between the vitamin D deficient group (group 1) and the no deficient group (group 2). Insulin resistance was estimated using the homeostatic model assessment for insulin resistance (HOMA-IR).
Results: The study population included 575 boys and 477 girls. Vitamin D deficiency was present in 56.0% of the study population (49.9% of boys, 63.4% of girls). Waist circumference and body mass index did not differ significantly between groups. Although fasting blood sugar levels were not different between groups, HOMA-IR was higher in group 1 than in group 2, 3.4±0.1 and 3.0±0.1, respectively. Sex-based differences included higher HOMA-IR and triglyceride levels in girls than in boys with vitamin D deficiency. Regression analysis revealed that HOMA-IR was associated with vitamin D deficiency in girls, odds ratio was 1.172 (confidence interval, 1.023-1.342).
Conclusions: Vitamin D deficiency is prevalent in Korean children aged 10-12 years, especially girls. Vitamin D deficiency may be associated with an increased risk of type 2 diabetes in Korean girls.

P1-d2-459 Glucose Metabolism 5

Abstract has been withdrawn

P1-d2-460 Glucose Metabolism 5

Mutations of monogenic forms of diabetes, especially INS gene mutation, in Japanese children with type 1B diabetes

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Background: The etiology of type 1 diabetes (T1D) is divided into two subtypes: type 1A (autoimmune-mediated) and type 1B (non-autoimmune-mediated). The genetic cause of type 1B diabetes in Japanese individuals is far from understood.
Objective and hypotheses: The aim of this study was to test for monogenic forms of diabetes in auto antibody-negative Japanese children with T1D.
Methods: SIxty six unrelated Japanese children with glutamate decarboxylase (GAD) 65 antibodies and/or IA-2A-negative T1D and diabetes diagnosed at < 15 yr of age were recruited from 17 unrelated hospitals participating in the Japanese Study Group of Insulin Therapy for children and adolescent diabetes (JSGIT). We screened the INS, HNF1A and the KCNJ11 gene by direct sequencing.
Results: We identified three novel (C31Y, C96R, and C109F) mutations and two previously reported mutations (R89C and G32S) in the INS gene in six children, in addition to one mutation in the KCNJ11 gene (H46R) in one child and two mutations in the HNF1A gene (R131Q and R203S) in two children. These mutations are most likely pathogenic and therefore the cause of diabetes in carriers. The onset age of diabetes in INS gene mutation is < 5 yr in five children and 7y in a child . That is 3m in KCNJ11 mutation and 8, 10 yr in HNF1A mutation.
Conclusions: Our results suggest that monogenic forms of diabetes, particularly INS gene mutations, can be detected in Japanese patients classified with type 1B. Mutation screening, at least of the INS gene, is recommended for Japanese patients diagnosed as autoantibody negative at < 5 yr of age.

P1-d2-461 Glucose Metabolism 5

Physical activity, fitness and screen time in childhood: how these lifestyle habits predict insulin sensitivity 2 years later

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Background: Understanding the impact of physical activity, fitness and sedentary behaviors on abnormal glucose metabolism is essential to the development of effective preventive strategies against type 2 diabetes mellitus. No longitudinal studies in youth examine the combined impact of these risk factors.
Objective: To determine the how fitness, moderate to vigorous physical activity (MVPA) and screen time (ST) predict insulin sensitivity (IS) over a 2 year period in a cohort of children with a family history of obesity.
Methods: Children from the QUALITY cohort (n=630), a prospective study of children with at least one obese biological parent, were assessed at baseline (age 8-10 years) and 2 years later. IS was measured by a fasting index (HOMA-IR) and an OGTT-based index (Matsuda-ISI). Fitness was measured by VO_{2peak}; percent fat mass (PFM) was measured by DXA; MVPA was measured using accelerometry. Screen time (ST) was measured by average daily hours of self-reported television, video game or computer use. Multivariable linear regression models were adjusted for age, sex, season and pubertal stage.
Results: Higher baseline MVPA and lower baseline ST predicted better IS (both measures) at time 2, however this impact was attenuated and no longer significant when baseline PFM was taken into consideration. Risk factors at time 2 appeared to be more strongly related to IS at that time: higher fitness and lower PFM were independently associated with better IS. Furthermore, higher ST was associated with better insulin sensitivity as measured by HOMA-IR, but not by Matsuda-ISI.
Conclusions: While MVPA and ST are important in predicting, over 2 years, IS in youth with a family history of obesity, their effect is mediated by adiposity. Current lifestyle habits appear to have a more important influence on IS in this population.

P1-d2-462 Glucose Metabolism 5

Use of metformin in paediatric patients with type 1 diabetes mellitus (T1DM): an analysis based on a German/Austrian pediatric registry for the German/Austrian DPV Initiative and the German BMBF competence networks diabetes and obesity

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Background: With increasing obesity in childhood, weight gain and insulin resistance become more frequent in type 1 diabetes (T1DM) patients. Especially during puberty, insulin therapy often has to be intensified in these patients and higher insulin doses are necessary. Some patients receive additional metformin to overcome the insulin resistance state, even if this drug is not officially recommended in T1DM.
Methods: Auxological and treatment data from 53.532 patients aged < 21 years with T1DM in the German/Austrian DPV registry were analyzed by multivariable mixed regression modeling. Results are indicated as mean and interquartile range.
Results: In our cohort 450 patients received additional metformin. These patients were predominantly female (61.1% vs. 47.2%; $p< 0.01$) and older as T1D-patients on insulin only: (15.6 [13.9 - 17.6] vs. 14.1 [11.4 - 17.5] years). They had a higher BMI-SDS (+1.86 [+1.33 - +2.58] vs. +0.52 [-0.11 - +1.16]; $p < 0.01$) and HbA1c (9.0 % vs. 8.6%, $p< 0.01$). Obesity was found in 52.9% of patients with adjunct metformin. Hypertension (21.1% vs. 9.8%) and dyslipidemia (59.4% vs. 40.3) were more frequent (both $p< 0.01$). Adjusted insulin dose was not significantly different (0.83 vs. 0.82 IU per kilogram bodyweight). Longitudinal data from 224 patients showed that additional therapy with metformin resulted in minor but not significant improvement of BMI-SDS (-0.01 [-2.01 - +1.19]) and reduction of insulin dose (-0.005 [-1.52 - +3.11]), but did not improve HbA1c by mean treatment period of 1.44 years.
Conclusions: Additional metformin therapy is used in T1DM patients with clear characteristics. These patients are more often obese and predominantly female. In our analysis additional therapy with metformin resulted in minor benefits compared to insulin therapy only.

P1-d2-463 Glucose Metabolism 5

Diagnostic and management in 33 focal forms of congenital hyperinsulinism - limits of the ^{18}F-DOPA PET/CT

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Background: Congenital hyperinsulinism (CHI) is a rare metabolic disease, which leads to hypoglycaemia due to uncontrolled insulin secretion of hyperactive beta-cells. Based on histological findings focal-forms, which can be cured by surgery, are differentiated from non-focal forms, in which blood-glucose levels have to be controlled by medicaments in the first place. To distinguish between these two forms, genetic analysis of ABCC8 and KCNJ11 and ^{18}F-DOPA PET/CT are of importance.
Methods: 33 CHI patients were diagnosed with focal CHI pre-operative by genetic analysis, ^{18}F-DOPA PET/CT and finally by histology of pancreatic biopsies. If the histology confirmed the presence of a focal form, surgery was performed to remove the focus.
Results: Patients were selected by focal enhancement of ^{18}F-DOPA tracer in PET/CT imaging. Mutations in ABCC8 were found in 20 patients (66%) an, 1 patient had a mutation in KCNJ11 (3%) and in 2 patients no mutation were found. In this cohort the specificity of the ^{18}F-DOPA PET/CT to differentiate focal from diffuse CHI was 100 % as described before. However in 3 patients the true focus size determinated by intra-operative histology differed extremely from the estimated expansion in the PET/CT. In all 3 patients giant-focal forms (> 75% of pancreas mass) were found which were difficult to be removed by the surgery while the focus size was underestimated by ^{18}F-DOPA-PET/CT.
Conclusion: We describe the phenotypes and management of 33 CHI patients with focal CHI. Although the ^{18}F-DOPA PET-CT had a specificity of 100% in recognizing a focal form in 3 patients the focus size was underestimated dramatically. These cases point out the limits of the present diagnostic approach especially in very large focal forms. Further research in alternative PET-tracers is needed to visualize the true beta-cell mass/activity.

P1-d2-464 Glucose Metabolism 5

Higher insulin detemir doses are required for the similar glycaemic control: comparison of insulin detemir and insulin glargine in children with type 1 diabetes

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Background: Insulin glargine and detemir are the most commonly used basal insulins in children with type-1 diabetes mellitus (T1DM).
Objective: To compare HbA1c and insulin doses in children with T1DM who receive glargine and detemir as basal insülin.
Method: This retrospective study included 119 (60 male, 59 female) children and adolescents with T1DM older than 4 years of age, minimum diabetes duration of 2 years and receiving basal-bolus insülin regimen (at least 4 injection/day). The average HbA1c for the previous year, the latest daily insulin doses, BMI SDS and other relevant data were obtained. Comparisons were made for those receiving glargine (n=84) or detemir (n=35) insülin as the basal insulin.
Results: Age, pubertal status, BMI SDS and diabetes duration were similar in glargine and detemir groups. Glycemic control was similar in both groups (HbA1c 8.6±1.6 vs. 8.8±2.0, respectively for glargine and detemir). Both basal insulin (0.41 vs. 0.55 U/kg/day) and total daily insulin (TDI) (0.95 vs 1.16 U/kg/day) doses were lower in the glargine group. Use of single daily basal insülin injection were more common in the glargine group.

	Glargine (n=84)	Detemir (n=35)	Total (n=119)	p
Age (years) mean±SD (range)	11.8±3.8 (6.0-18.2)	11.6±3.6 (5.2-18.0)	11.7±3.8 (5.2-18.2)	0,855
HbA1c(%) mean±SD (range)	8.6±1.6 (5.7-14.8)	8.8±2.0 (6.2-15.8)	8.7±1.7 (5.7-15.8)	0.579
Basal/total insulin ratio mean±SD (range)	0.43±0.09 (0.25-0.61)	0.47±0.09 (0.29-0.64)	0.44±0.09 (0.25-0.64)	**0.000**
Total insulin dose per kg (U/kg) mean±SD (range)	0.95±0.21 (0.53-1.57)	1.16±0.28 (0.63-1.78)	1.01±0.25 (0.53-1.78)	**0.000**
Basal insulin injection Once daily n (%)	61 (72.6)	12 (34.3)	73 (61.3)	**0.000**

[Parameters of patients due to basal insulin group]

When the patients were subdivided according to puberty, prepubertal patients, glargine and detemir groups had similar HbA1c levels (8.5±1.2 vs 8.2±1.3, p:0.612) but glargine group had lower TDI dose(0.95±0.20 vs 1.11±0.25 U/kg, p:0.047). In pubertal patients, glargine group had slightly lower HbA1c levels (8.7±1.8 vs 9.3±2.3, p:0.40) and again lower TDI dose (0.95±0.20 vs 1.20±0.30 U/kg, p:0.001).
Conclusion: Detemir provides similar glycemic control with glargine, but, approximately 20% higher doses and twice daily injection is required.

P1-d2-465 Glucose Metabolism 5

Use of glucagon-like peptide 1 (GLP-1) receptor agonists in Prader-Willi syndrome: report of six cases

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Background: Glucagon-like peptide 1 (GLP-1) receptor agonists Liraglutide (Lrg) and Exenatide (Exn) are a new class of drugs recently introduced for Type 2 Diabetes Mellitus (T2DM) treatment that reduce appetite and body mass. Very little is known about use of these compounds in Prader Willi Syndrome (PWS).
Objective: We report a short term Lrg or Exn treatment in six genetically confirmed PWS patients with T2DM.
Patients: Patients were treated at least 12 months with metformin or glicazide (met:1700 to 3000 mg/d; glic: 30 mg/d) before starting therapy with GLP-1 agonists (Lrg 1.2 to 1.8 mg/d or Exn 20 mg/d). Three suffered hypertension and hypertrigliceridemia, one hypercholesterolemia, all had a liver steatosis. One was on testosterone, one on estrogens. None of them experienced GH therapy.
Results: Improvement in glycemic control as documented also by continuous monitoring system was observed. Four experienced a decrease (although not statistical) in HbA1c, BMI and WC, while two only showed stable BMI and decreased WC, more than diet and met alone. No side effect were observed.

	BASAL	BASAL	BASAL	12 months	12 months	12 months	24 months	24 months	24 months
Pts (SEX-years) THERAPY	BMI	HbA1c%	WC (cm)	BMI	HbA1c%	WC (cm)	BMI	HbA1c%	WC (cm)
1 (M-37.3) Lrg+Met	35.9	7.6	116	33	6.3	100			
2 (M-20.7) Exn+Met	28	8.2	105	26.5	6.8	101.5			
3 (M-27.7) Lrg+Met	44.3	7.5	135	42.6	6.9	131			
4 (F-30.4) Lrg+Met	49.6	8.7	140	48.4	7.3	137.5	48.1	7.8	136.5
5 (F-37.1) Lrg+Met+glic	30.1	8.3	100	30.7	8.6	102	30.2	9.3	99
6 (F-34.5) Lrg+Met	57.2	9.5	150	58.5	9.5	152	58.2	10.1	146

[table 1]

Conclusion: Use of GLP1 agonists in PWS with T2DM seems to improve glycemic control and reduce BMI although a longer follow up is needed to evaluate the long-term effect of these new compounds in these patients.

P1-d1-466 Growth 1

FGF21 causes GH resistance in human chondrocytes through activation of SOCS2 and inhibition of IGF-1 expression

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Background: Fibroblast growth factor 21 (FGF21) is a key metabolic regulator in the adaptation to fasting. In food-restricted mice, inhibition of skeletal growth appears to be mediated by the antagonistic effect of FGF21 on GH action in the liver and in the growth plate (Yu et al., 2012, Kubicky et al., 2012). The role of FGF21 in growth regulation in humans is currently unknown.
Objective and hypotheses: To provide mechanistic insights into the reduced caloric intake associated with GH insensitivity and growth failure we hypothesized that FGF21 inhibits GH action in human chondrocytes by blocking post-receptor GH signaling.
Methods: We established chondrocyte primary cultures from costal cartilage of pediatric patients undergoing reconstructive surgery. We first assessed the integrity of the GH-receptor and IGF-1 receptor signaling by Western Blotting, and expression of the FGF21 receptor complex by RT-PCR. Next we tested the effect of recombinant FGF21 on basal and GH-induced *Suppressor of cytokine signaling 2* (*SOCS2*) expression, basal and GH-induced *IGF1* expression by qPCR, and basal and GH/IGF1-induced cell proliferation by Methylene Blue assay.
Results: Human chondrocyte cultures expressed GH-receptor and responded to recombinant to GH and IGF1 through phosphorylation of ERK 1/2, AKT and STAT5, and expressed the complex FGFR1c/bKLOTHO, the preferred FGF21 receptor. FGF21 significantly up-regulated basal and GH-induced *SOCS2* expression. FGF21 also inhibited GH-induced *IGF1* expression and cell proliferation, but did not affect IGF1-induced cell proliferation.
Conclusions: FGF21 blocks GH action in human chondrocytes by inhibiting post-receptor signaling involving induction of *SOCS2* and inhibition of *IGF1* expression. These data provide a new mechanistic insight into GH resistance secondary to reduced caloric intake.

P1-d1-467 Growth 1

Duplication of the NSD 1 (Sotos) gene causes the reverse phenotype of short stature and IUGR

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Background: Haploinsufficiency of the nuclear receptor binding SET domain protein 1(NSD 1) is the major cause of Sotos syndrome, characterised by overgrowth, learning difficulties and tumour susceptibility. We report a reverse phenotype: a patient with intrauterine growth restriction (IUGR), severe post natal growth failure and learning difficulties in whom array CGH detected a duplication of the 5q35.2q35.3 region encompassing the NSD1 gene.
Case: At 3.3 years a girl was referred for endocrine assessment with extreme symmetrical short stature and history of hypoglycaemia (HeightSDS -5.9; weightSDS -7.1). Dysmorphic features included bifid thumb, sacral pit, accessory auricle, short narrow palpebral fissures and duane anomaly. She had moderate learning difficulties. She had been born at 37/40 with IUGR (weightSDS -3.5). Hypoglycaemia in the neonatal period had been investigated with no metabolic abnormality found.
A Glucagon test which demonstrated normal GH (peak 14.7mcg/l) and cortisol responses (peak 1078mmol/L). Height velocity(HV) was 4 cm/yr. She was started on GH treatment (small for gestational age indication) with good response (HV 9.8 cm/yr in 6 months). She also required thyroxine for central hypothyroidism (FT4 11.8 pmol/l, TSH 1.6mu/L).
Genetics investigations included an array CGH which identified a duplication of 5q352q353, also present in her mother who was short (heightSDS, -2.3) but had no other anomalies or developmental problems.
Conclusion: NSD 1 haploinsufficiency due to either deletion or intragenic mutation is associated with Sotos syndrome characterised by overgrowth and hypotonia. Duplication of NSD-1 may be associated with a variable reverse phenotype ranging from moderate short stature alone (mother), to severe growth failure with developmental delay and dysmorphic features . This case highlights the importance of array CGH in the investigation of growth failure and adds to our understanding of the role of NSD-1 in growth.

P1-d1-468 Growth 1

Designing informative growth charts for specialist use. A novel evidence-based approach using two methods to evaluate pubertal progress

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Background: Depicting the progress of puberty graphically can prove challenging. The 2012 UK 2-18 years Growth Charts incorporated the new simpler rating system of Phases of Puberty represented on the chart by the Puberty Lines. However in specialist and paediatric endocrine clinics the more detailed Tanner system may be preferable, but previous attempts to represent pubertal progress graphically were unsatisfactory.
Objective and hypotheses: To consider and evaluate the van Buuren 'puberty plot' stage line diagrams, a novel type of reference diagram designed for tracking developmental processes over time.
Methods: This system uses transition probabilities between successive stages modelled as smoothly varying functions of age. Age-conditional references are calculated from the modelled probabilities by the mid-P value, eliminating the influence of age by calculating SDS. This method had been published using data from 3028 girls and 2525 boys in the 4th Dutch Growth study to produce reference charts on secondary sexual maturation. These stage line diagrams were re-evaluated using examples of natural variations of pubertal tempo in 80 girls from the Edinburgh Longitudinal Growth Study. Puberty reference chart usability was then tested on final year medical students.
Results: 91% were able to plot the chart accurately with 72% finding the approach straightforward. 57% found interpretation easy and 15% difficult. Plotting accuracy was 100%, but 14% misinterpreted the centile scales.
Conclusions: The stage line diagram is a highly useful instrument for tracking pubertal development processes over time. This new approach is therefore a workable tool which can therefore be incorporated into specialist growth charts such as the new UK Childhood and Puberty Close Monitoring chart (2013) alongside the existing Puberty Phase lines.
(1) www.growthcharts.rcpch.ac.uk
(2) van Buuren S, Statist. Med. 2009; 28:1569.

P1-d1-469 Growth 1

Evaluation of submicroscopic chromosomal deletions and duplications in dysmorphic patients born small for gestational age

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Background: The etiology of prenatal onset growth retardation with postnatal persistence is heterogeneous, often encompassing complex genetic disorders of difficult diagnosis.
Objective and hypotheses: To analyze the frequency of submicroscopic chromosomal deletions and duplications in a group of patients born small for gestational age (SGA) without a known cause.
Methods: We evaluated 48 patients with pre and postnatal growth retardation associated to other physical or developmental defects (dysmorphic features or intellectual disability), but without criteria for the diagnosis of known syndromes. We performed an array-based comparative genomic hibridization (aCGH) with DNA from all patients. We compared the results with copy number variations (CNVs) already described in normal controls databases and we evaluated 25 relatives for familial segregation.
Results: We identified 15 CNVs in 14 of the 48 patients (29%). None of these imbalances has been reported in healthy individuals. Considering their sizes, their gene contents and their familial segregations, we categorized at least 7 CNVs, found in 6 patients (I to VI), as probably pathogenic. These imbalances and their sizes were as follows: I) a 1.6Mb dup(10)(q26.2;26.3) and a 4.5Mb del(10)(q26.3); II) a 2.5Mb del(22)(q11.21); III) a 2.5Mb dup(5)(q21.3); IV) a 0.4Mb del(20)(p13); V) a 3.5Mb del(3)(q27.1;q27.3); VI) a 2.7Mb dup(14)(q11.2;q12). Of the other imbalances found, we categorized 4 as variants of uncertain significance and 4 as benign.
Conclusions: We conclude that the frequency of pathogenic CNVs in patients born SGA associated with dysmorphic features or intellectual disability was high (at least 13%) in this study, showing the probable importance of aCGH as a clinical genetic test to clarify the diagnosis of these patients and to identify new chromosomal regions implicated in this condition.

P1-d1-470 Growth 1

Recombinant growth hormone increases intact FGF23 level

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Background: We previously demonstrated a positive association between intact FGF23 and IGF1 levels in children with normal renal function. Since recombinant growth hormone (rhGH) increases IGF1 levels, we hypothesized that such a therapy could also increase FGF23 levels.
Methods: We performed a before/after clinical trial in 14 children (9 boys, mean age 10±4 years, mean height SDS -1.6±1.2, mean estimated GFR 108±19 mL/min/1.73m^2), assessing uric acid, parathyroid hormone (PTH), C-terminal FGF23 (2nd generation Immutopics), intact FGF23 (Kainos) and IGF1 (CIS-bio) circulating levels just before and six months after starting rhGH for GH deficiency (n=6) or intra-uterine growth retardation (IUGR). Non-parametric Wilcoxon paired and Mann-Whitney tests were used (SPSS17.0).
Results: At baseline, median(range) IGF1, C-terminal FGF23 and intact FGF23 levels were 135(12-510) µg/L, 25(14-52) RU/mL and 28(20-49) pg/mL, respectively; 6 months after rhGH, they were 329(55-1039) µg/L, 27(15-57) RU/mL and 34(26-60) pg/mL, respectively. The increase of IGF1 and intact FGF23 levels was significant (p= 0.001 and p=0.045, respectively); in contrast, there were no differences for C-terminal FGF23, uric acid and PTH. When comparing GH-deficient and IUGR children at baseline, there were no differences for age and height-SDS but BMI was significantly lower in IUGR children (p= 0.017). After 6 months on therapy, there were no differences in terms of delta-IGF1, delta-FGF23 (both types), delta-uric acid and delta-PTH in the two groups.
Conclusions: In children receiving rhGH therapy for GH deficiency or IUGR, rhGH increased intact but not C-terminal FGF23 levels six months after the beginning of therapy. Because increased FGF23 levels were associated with cardiovascular mortality in chronic kidney disease, these results suggest to monitor FGF23 levels in patients receiving rhGH, particularly if they have associated cardiovascular risks.

P1-d1-471 Growth 1

Impaired growth hormone signaling pathway in fibroblasts of children with chronic renal failure under peritoneal dialysis therapy. Preliminary data

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Background: Growth retardation is still a critical problem in chronic renal failure(CRF) children under peritoneal dialysis (PD) therapy. GH resistance has been described and many mechanisms have been proposed including impaired intracellular postreceptor GH signaling.
Objective: To study the effect of hGH stimulation on JAK 2 and STAT 5b phosphorylation in CRF children under PD therapy and compared it with a healthy control group.
Hypotheses: CRF children on peritoneal dialysis has impaired intracellular GH signaling.
Methods: We studied 17 CRF prepuberal children, (9 boys), 5.7±4.3years and 20 healthy prepuberal children (16 boys) 4.5±1.58 years. Fibroblasts cultures were prepared from skin sample and at 80% confluence, after 48 hours serum deprivation, 200ng/ml hGH stimulation was done for 30 and 60 min. Cytoplasmic (cyt) and nuclear fractions were purified and the expression of total (t) and phosphorylated (p) JAK-2 and STAT-5b were studied by Western blot.

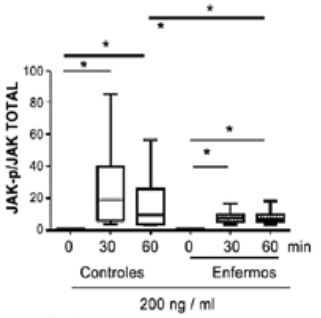

Fig 1.

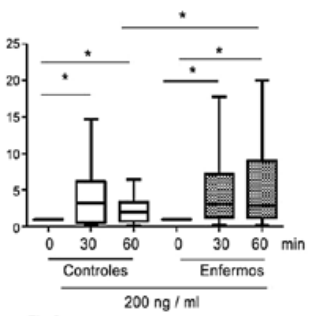

Fig 2.

*p<0.05

[Jak-2 and Stat 5b results]

Results: A significant decrease in cytoplasmic p-JAK2 (Fig.1) and no differences in cytoplasmatic and nuclear pSTAT 5b were observed in CRF patiens vs controls. hGH induce nuclear traslocation of p STAT 5b in CRF and control children, with significant highest levels of nuclear/cyt pSTAT 5b ratio at 60 min (Fig2) in CRF patiens.
Conclusions: These results suggest that intracellular growth hormone signaling is impaired in CRF children, probably contributing to growth failure. This results are the first intracellular GH-signaling in pediatric patients under chronic peritoneal dialysis.

P1-d1-472 Growth 1

Individuals heterozygous for the c.424_427del *STAT5B* mutation have mild growth and immunological phenotypes

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Background: STAT5b is a protein involved in the signaling pathway of growth hormone (GH) and interleukins. Homozygous inactivating mutations in *STAT5B* gene cause GH insensitivity with chronic pulmonary disease and/or other immune dysfunctions. The effect of heterozygous *STAT5B* mutations on phenotype is still poorly characterized.
Objective and hypotheses: To analyze if a heterozygous *STAT5B* mutation could cause an intermediate phenotype between patients with homozygous mutations and controls.
Methods: Thirty-four direct relatives of two patients homozygous for the c.424_427del *STAT5B* mutation were evaluated. We compared clinical and laboratory characteristics between relatives heterozygous for the *STAT5B* mutation and non-carriers.
Results:

	Homozygous (n=2)	Heterozygous (n=14)	Wild type (n=20)	p*
Height SDS	-6.4 / -4.7	-0.9 ± 0.6	0 ± 1.1	0.008
Basal GH (µg/L)	8.7 / 0.2	1.7 ± 2.2	1.5 ± 2	ns
IGF-1 SDS	-3.6 / -3.5	-0.5 ± 1.1	0.2 ± 1.1	0.069
IGFBP-3 SDS	-4.6 / -4	-1.4 ± 1.5	-0.6 ± 1.4	ns
Prolactin (ng/mL)	34 / 37	13.2 ± 8.5	12.3 ± 8.3	ns
Respiratory allergy	100%	57%	40%	ns
Lymphocytes (cells/mm3)	1000 / 1000	1739 ± 368	2153 ± 558	0.022
IgG (mg/dL)	759 / 1013	1040 ± 177	1081 ± 166	ns
IgE (UI/mL)	2 / 3	350 ± 423	167 ± 228	ns

[Table 1]

* Statistical difference between individuals heterozygous for the STAT5B mutation and non-carriers; ns non significant.
Interestingly, two relatives heterozygous for this *STAT5B* mutation were diagnosed with "idiopathic" pulmonary fibrosis.
Conclusions: Individuals heterozygous for the studied *STAT5B* mutation are shorter than their non-carrier relatives, although in the normal height range. They tended to have lower IGF-1 SDS and more respiratory allergy. A significant decrease in lymphocytes count was also observed in carriers. These results suggest a mild phenotype in individuals heterozygous for *STAT5B* mutations, but it is still necessary to study more relatives in this and other families to confirm the present findings.

P1-d1-473 Growth 1

Short stature and severe insulin resistance associated with double heterozygous mutations of *IGF1R* and *INSR* genes: a physiologic role of IGF1R-INSR hybrids in longitudinal growth?

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Background: Insulin and IGF1 receptors (INSR, IGF1R) are constituted by heterodimers formed by an α and a β subunit. INSR and IGF1R can form hybrids that bind IGF1with higher affinity than insulin. Heterozygous, dominant-negative INSR mutations give rise to severe insulin resistance type A (SIR-A), characterized by hyperinsulinemia and hirsutism in adolescent females of normal stature. Mutations of IGF1R can cause short stature.
Objective and hypotheses: Establish the genetic basis of severe insulin resistance and short stature in two sisters with SIR-A.
Methods: Dna direct sequencing. Studies on fibroblasts.
Results: In two lean sisters, 21 and 16 yrs old, with SIR-A (post-load insulinemia: 2100 mU/ml, severe hirsutism) and short stature (133 and 138 cm, respectively) we identified the heterozygous INSR p.Gly1146Arg mutation, that was paternally inherited (poast-load insulin=692 mU/ml). This mutation was already described in a girl of normal stature with SIR-A. Screening of *IGF1R* gene revealed that both sisters bear the novel p.Val422Asp heterozygous mutation (PolyPhen2: damaging, score of 0.994) , inherited from their mother, 149 cm tall. A younger sister,12 yrs old, with normal INSR/IGF1R genotype, is 151 cm tall.
GFP-FOXO1 transfected in fibroblast of normal sister localized mainly in the cytoplasm and became more nuclear upon FCS starvation for 16 h while no effect was observed after FCS starvation of fibroblast of the two affected sisters with GFP-FOXO1 remaining mostly nuclear even after incubation with high dose insulin+IGF1. RNA micro-array and real-time PCR analysis revealed that IGF2 was underexpressed in fibroblasts of the affected sisters as compared to the younger sister and the father. INSR and IGF1R expression was normal.
Conclusions: We hypothisize that short stature of these two girls it is due to impaired biological activity of INSR/IGF1R hybrids. Experiments to demonstrate this mechanism are under way.

P1-d1-474 Growth 1

Are recent references for length/height influenced by the presence of overweigth or obese children?

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Background: Growth reference charts are usually based on samples of children free from known diseases that might affect growth. However, more recent samples often contain a significant porportion of children that are overweight or obese.
Objective and hypotheses: As obesity is known to affect linear growth, the question arises to what extent the presence of overweight or obese children in reference samples affects the percentiles curves and the limits of "normal" growth.
Methods: We analyzed a cross-sectional sample of children (n=6406) aged 2-19 years from the Bergen Growth Study collected in 2003-2006. Growth curves for length/height were estimated with the LMS methods, with and without children considered overweight or obese by the definition of the IOTF.
Results: The IOTF prevalence of overweight and obesity in our sample was 13.8% and 2.3% respectively. Obese boys and girls had an overall mean height of +0.16 and +.13 SDS, with a maximum of +0.63 and +0.7 SDS, occuring at ages 8 and 7 years respecively. Excluding overweight and/or obese

children had an impact on BMI-for-age curves, but effects on length/height were both visually and numerically small.
Conclusions: Excluding overweight or obese children from the reference sample had only a minor effect on the the length/height percentile curves. The references for height are therefore relatively unaffected by the current "obesity epidemic" in a population where 14% of the children are overweight or obese.

P1-d1-475 Growth 1

Factors affecting growth velocity after discontinuation of gonadotropin-releasing hormone agonist treatment in girls with central precocious or early puberty

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Background: Final height outcome after Gonadotropin-releasing hormone agonist (GnRHa) treatment in girls with central precocious puberty (CPP) is known to be associated with various clinical factors including growth after discontinuation of GnRHa treatment.
Objective and hypotheses: The purpose of this study was to analyze growth velocity (GV) after discontinuation of GnRHa treatment in girls with CPP or early puberty and to identify clinical or laboratory factors associated with changes in GV.
Methods: We analyzed clinical and laboratory data of 56 girls with CPP (n=43) or early puberty (n=13) who were treated with GnRHa.
Results: GV during the first year after discontinuation of GnRHa (5.8±1.6 cm/yr) increased significantly compared to GV during the last year of treatment (4.9±1.1 cm/yr) (P=0.001). GV during the first year after discontinuation of treatment was positively correlated with mid-parenteral height standard deviation score (SDS) (r=0.419, P=0.002), height SDS for bone age (BA) at discontinuation of treatment (r=0.443, P=0.001) and predictive adult height at discontinuation of treatment (r=0.317, P=0.024). GV during the first year after discontinuation of treatment was negatively correlated with chronological age (CA) at start of treatment (r=-0.339, P=0.011), BA at start of treatment (r=-0.381, P=0.004), peak LH/FSH (r=-0.527, P=0.001) and pubertal stage at start of treatment (r=-0.362, P=0.007). In multiple linear regression analysis, lower BA at start of treatment (β=-0.321, P=0.020) and higher height SDS for BA at discontinuation of treatment (β =0.933, P=0.006) were associated with higher GV during the first year after discontinuation of treatment.
Conclusions: These data suggest that BA at start of treatment and height SDS for BA at discontinuation of treatment are factors predicting increase in GV during the first year after discontinuation of GnRHa treatment.

P1-d1-476 Growth 1

The easypod™ connect observational study (ECOS): adherence to recombinant human growth hormone (r-hGH) therapy in younger and older children

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Background: Patient age can affect adherence to growth hormone (GH) therapy. The ECOS study is following patients receiving r-hGH for up to 5 yrs.
Objective and hypotheses: To compare adherence rates in prepubertal and adolescent patients receiving treatment with r-hGH.
Methods: Demographic, auxological and diagnostic data were obtained from medical notes, and adherence data were uploaded from auto-injectors. Treatment adherence rate was defined as the number of days with injections/planned injection days during the study period, expressed as %. In this interim analysis, adherence data collected up to 12 months of study inclusion are presented and compared by age groups approximating prepubertal and adolescent stages (girls: < 10 vs ≥10 yrs; boys: < 12 vs ≥12 yrs) using two-sample Wilcoxon signed-rank testing.
Results: Data were available for up to 416 patients (girls: n=77 < 10 yrs, n=96 ≥10 yrs; boys: n=155 < 12 yrs, n=88 ≥12 yrs). Median (Q1; Q3) adherence rate (%) at each time point for girls and boys are tabulated.

	Girls		Boys	
	<10 yrs	≥10 yrs	<12 yrs	≥12 yrs
Up to M3	97.4 (89.0; 100.0) n=77	94.7 (84.1; 98.7) n=96	96.2 (90.1; 98.9) n=155	89.9 (84.1; 97.8) n=88
Up to M6	97.0 (92.1; 99.4) n=48	92.1 (81.9; 97.4) n=62	96.5 (89.1; 98.7) n=102	90.0 (82.4; 96.8) n=58
Up to M9	96.3 (89.0; 99.1) n=23	87.3 (67.4; 97.1) n=39	95.7 (87.2; 98.7) n=56	90.8 (59.3; 94.0) n=31
Up to M12*	93.6 (82.4; 99.0) n=13	86.5 (64.4; 95.2) n=24	94.4 (86.5; 98.1) n=34	85.3 (74.7; 92.6) n=13

M, month.*p-values for comparisons up to Month 12 = 0.0948 (girls <10 vs ≥10 yrs), 0.0062 (boys <12 vs ≥12 yrs).

[Table]

Conclusions: Lower adherence to r-hGH therapy was observed in older than younger children (girls aged ≥10 and boys aged ≥12 yrs, than those < 10 or < 12 yrs, respectively). These data suggest that patients are less adherent when approaching adolescence; this may potentially compromise treatment effect, so additional support to optimize treatment outcomes could be considered.

P1-d1-477 Growth 1

Cardiofaciocutaneous syndrome, a Noonan syndrome related disorder: clinical and molecular findings

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Background: Noonan syndrome (NS) and related disorders such as cardiofaciocutaneous syndrome (CS) have been referred to as "neuro-cardio-faciocutaneous syndromes" (NCFCS) as they all share phenotypic characteristics and are considered the result of dysregulated RAS-MAPK signaling.
Objective and hypotheses: To describe 10 patients with CS and compare them with 130 patients with other NCFCS.
Methods: Clinical data from patients submitted for genetic analysis were collected using a data base. Bidirectional sequencing analysis of *PTPN11*, *RAF1*, *SOS1* and *BRAF* focused on exons carrying recurrent mutations was performed. Clinical characteristics from 2 patients with mutations in *BRAF* and *MAP2K1* genetically diagnosed in another laboratory were included.
Results: Phenotypic characteristics and mutations found in the 8 patients with genetic analysis performed in are laboratory are summarized in table 1.

Age in years	Sex	Height in SDS	Heart defect	Crypt-orchidism	Ectodermal anomalies	Develop-mental delay	MRI anomalies	Mutation in BRAF
2	Female (F)	-4.3	Normal	-	Present	NA	NA	Gln257Arg
2	Male (M)	-2.95	Pulmonary valve steno-sis (PVS)	Present	Not available (NA)	Present	NA	Glu501Lys
4	M	-2.84	PVS	Present	Present	Present	Present	Glu501Lys
3	M	-2	Hypertrophic cardio-myopathy (HCM)	Present	Present	Present	Present	Asn581Asp
4	F	-2	PVS	-	No	No	No	Gln257Arg
2	F	-3.02	HCM	-	No	Present	Present	Leu485Phe
1	M	-3.1	PVS+HCM	No	Present	Present	NA	Ala246Pro
1	F	-2.82	PVS	-	No	Present	No	Gln257Arg

[Clinical and molecular findings summary]

Short stature, hypoacusia, developmental delay and ectodermal anomalies were more frequent in CS patients when compared with the rest of NCFCS patients. Feeding problems were more prevalent among CS patients without reaching stadistic significance. In at least two cases molecular testing helped reconsider the diagnosis.
Conclusions: Molecular genetic testing is a valuable tool for differencial diagnosis of NS and NS related disorders. Our CS patients showed a rather severe phenotype but at least one patient showed no developmental delay, which illustrates the variability of the phenotypic spectrum caused by *BRAF* mutations.

P1-d2-478 Growth 2

Whole exome sequencing is an effective tool for discovering the genetic causes of familial endocrine disorders

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Background: Recent technological developments, like the possibility to sequence an individual's complete genome or exome in one experiment, allow for determining the genetic cause of a patients' phenotype. We used this approach in 6 families in which the genetic cause of the phenotype could not be determined with the candidate gene approach
Objective: To determine the diagnostic yield of whole exome sequencing (WES) in 6 families with paediatric endocrine disorders.
Methods: The exome of 28 individuals from 6 families with different phenotypes was sequenced and the variants were filtered for pathogenic mutations that could explain the clinical phenotype. Presenting features included short stature, tall stature, morbid obesity and common variable immunodeficiency syndrome.
Results: In 4 out of 6 families the causative mutation could be identified. In one family with autosomal dominant inheritance of proportionate short stature a novel heterozygous missense mutation in *FGFR3* (p.Met528Ile) was identified. In another family, consisting of 2 brothers with spondyloepimetaphyseal dysplasia, compound heterozygosity for a missense and a frameshift mutation in *PAPSS2* was detected. In a girl with morbid obesity compound heterozygosity for a missense and splice site mutation in *LEPR* was found, and a heterozygous mutation in *NPR2* was identified in a man with extreme tall stature. In one case with isolated short stature no clear candidate gene was detected. In a family consisting of three children with common variable immunodeficiency a heterozygous mutation in *TNFRS13B* was found, however, this did not cosegregate with the phenotype. Knowledge on the pattern of inheritance and sequencing of multiple individuals in one family greatly helped in identifying the pathogenic mutation through variant filtering.
Conclusion: WES is a powerful tool in determining the causative mutation in patients in whom the candidate gene approach failed.

P1-d2-479 Growth 2

QEPS - a new mathematical model describing individual human growth

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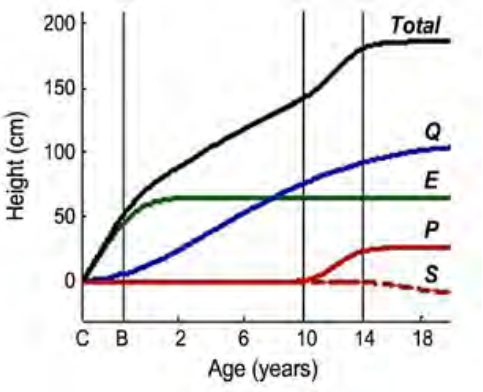
Background: Longitudinal spontaneous human growth from fetal period to adult height often shows systematic nonparallel growth in SD-scores. Systematic modeling of nonparallel growth in SD-scores is lacking.
Objective and hypotheses: To develop a new model describing the growth from fetal life to adult height. To model individual growth changes in SD-scores, with a limited number of parameters and to quantify the occurrence of nonparallel growth.
Method: Longitudinal height is modeled on the cohort from the Swedish growth reference (born 1974, n=3650). The growth values can be described as a sum of four growth functions: *Quadratic(Q), Exponential(E), Pubertal(P)* and *Stopping(S)*.
Key individual parameters of the model expressed in height in cm are translated in corresponding parameters expressed in height SD-scores, addressing different growth periods. The model is tested on 712 girls and 727 boys from a cohort born 1990. Systematic nonparallel growth in SD-scores is classified by non overlapping 90% confidence intervals in SD-scores.
Result: In the prepubertal period 13%(14%) of the girls(boys) had nonparallel growth in SD-scores before 2 years of age and 19%(20%) after 2 years. For

the pubertal period we adjusted the SD-scores for the individual timing of puberty and still found 29%(25%) of the girls(boys) having pubertal nonparallel growth. Evaluating over the total growth period 62%(60%) of the girls(boys) had nonparallel growth.
Conclusion: The proposed QEPS model can concisely describe a wide variety of growth curves in SD-scores of healthy individuals. More than half of the individuals appear to have systematic nonparallel growth in SD-scores.



[Figure 1]

P1-d2-480 Growth 2

Reference values for IGF-I, IGFBP-3 and ALS in the diagnostic work-up for short stature

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Background: The measurement of IGF-I and IGFBP-3 has become a routine and often first- line testing in children with growth disorders, furthermore monitoring IGF-I levels during growth promoting therapy serves also for addressing safety issues. The role of serum ALS as a screening parameter for hetero- or homozygous mutations in the ALS gene has still to be determined, which has not been done so far due to lack of representative reference values.
Aim: To obtain reference values for IGF-I, IGFBP-3 and ALS using ELISA assays with recommended standards and to compare these references with those provided by the manufacturer.
Methods: 188 blood samples from children and adolescents were collected. The reference curves were fitted using GAMLSS models. A model for SDS calculation for each of the three parameters was fitted. Furthermore, we compared SDS values calculated with our generated formula against those obtained using the data delivered by the assay provider by Bland-Altman plots.
Results: Our data suggest that the IGF-I levels in males reach a peak later and describe a wider range of the normal interval than described in the literature. The ALS levels reach a peak around the age of 15 in girls and later-on in puberty in boys. The Bland-Altman plots show a rough agreement between the previous SDS calculation and our new one only for SDS around 1; for SDS at -2, a difference of 0,83SD was noticed.
Conclusion: We present the first ALS reference values using an ELISA assay for the pediatric population. Our IGF-I reference values are suitable for the diagnosis of low IGF-I states until the age of 10 years, after this age the wide range of measurements in the reference population represents some limitation in the accuracy of extremes like -2,0 SDS.

P1-d2-481 Growth 2

Does muscle training increase growth velocity in children with cerebral palsy?

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Background: Activation of the neuro-muscular system is one of the major factors influencing growth in children. The exact physiological pathways are not fully understood but the increase of muscle activity leads to an activation of the growth plates and stimulates growth. Most children with cerebral palsy (CP) have only limited possibilities to activate their muscles due to the central lesion resulting in impaired motor function and immobilisation. This lack of activity might be one of the reasons why these children are shorter and show reduced growth velocity (GV) compared to normally developing children.
Patients and intervention: 75 children (43m/32f; mean age 7.18 years) with CP and impaired motor function (GMFCS-level: I n=3; II n=11; III n=30; IV n=23; V n=8) were analysed. All of them were short of stature for their age with a mean SDS of -1.7 at start. They participated in the Cologne rehabilitation programme to improve their motor function. This training includes 3 weeks of intensive physiotherapy, 6 months of Whole Body Vibration (WBV) training (side-alternating Galileo System®) and 6 months of follow-up. After completion of the first programme they started a second program with only 4 months of training and 8 months follow up.
Results: The results of growth velocity (GV) during training and follow up periods are presented in Table 1.

	Training 6 months	Follow-up 6 months	Training 4 months	Follow-up 8 months
Mean GV [cm/year]	7.089	5.823	6.681	4.565
Std. Deviation	3.683	3.469	3.943	3.374
p-value	0.059		0.002	
p-value	0.124			

[Growth velocity]

Conclusions: This evaluation shows that an intensive training of the musculo-skeletal system for a period of 4 to 6 months with physiotherapy and WBV has a beneficial effect on GV in children with CP and severe impairments of motor function. Therefore muscle training might be included in the therapeutic spectrum regarding growth in handicapped children.

P1-d2-482 Growth 2

The sitting height/height ratio for age is a simple and useful tool to select children with idiopathic short stature for *SHOX* studies

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Background: *SHOX* haploinsufficiency causes a wide spectrum of short stature phenotypes, such as Leri-Weill dyschondrosteosis (LWD) and idiopathic short stature (ISS). The presence of abnormal body proportion, assessed by sitting height:height ratio for age and sex (SH/H-SDS), may be used to select patients for *SHOX* studies.
Objectives: To determine the frequency of disproportionate short stature using SH/H-SDS in normal and short children.

Subjects and methods: Height (H), sitting height (SH) and weight were evaluated in 1,771 healthy children, 128 children with ISS and 58 individuals with isolated SHOX defects (SHOX-D; 29 measurements obtained during childhood and 45 obtained during adulthood).
Results: Control children (from 4-14 yr, H-SDS=0.3 ± 0.9) had a SH/H-SDS of +0.1 ± 0.9. The frequency of abnormal body proportion, defined as SH/H-SDS > 2, was 1.4% (95%CI of 0.8 to 1.9%). In ISS children (age 10 ± 3.5 yr and H-SDS of -2.6 ± 0.7), mean SH/H-SDS was +0.7 ± 1.6. The frequency of disproportional short stature was 16.4% (95%CI of 10 to 22%), significantly higher than observed in controls ($p< 0.001$). *SHOX* gene was evaluated in all disproportionate ISS children and defect in this gene was observed in 19% of them, a frequency higher than in unselect ISS children (3%). In children with SHOX-D (age from 1 to 14 yr and height SDS of -2.0 ± 1.1), mean SH/H-SDS was 3.7 ± 1.6. Adults with SHOX-D had H-SDS of -2.7 ± 1.0 and mean SH/H-SDS of 4.0 ± 1.4. The frequency of disproportionate short stature in patients with SHOX-D was 89% (95%CI of 80 to 98%), regardless of phenotype at the evaluation (LWD or ISS).
Conclusion: Abnormal body proportion is uncommon in children with normal growth, but it is observed in 89% of patients with SHOX-D. Mutations in *SHOX* gene are identified in 19% of ISS children with SH/H-SDS > 2, showing that SH/H-SDS is a useful and simple tool to select ISS children to undergo *SHOX* molecular studies.

P1-d2-483 Growth 2

Current growth and metabolic syndrome components in Korean adolescents according to birth weight at gestational age: results from the Korea National Health and Nutrition Examination Surveys (KNHANES) 2010 - 2011

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Backgrounds: The fetal origins hypothesis states that individuals born small for gestational age (SGA) have a higher risk of metabolic syndrome (MS) later in life. In infants born SGA, there may be persistent short stature in adult.
Objective and hypotheses: The present study aimed to assess current growth and MS components in Korean adolescents according to BWGA.
Methods: This is a cross-sectional study. Data were obtained from the 5th Korean National Health and Nutrition Examination Survey (K-NHANES) conducted during 2010 - 2011 by the Korean Ministry of Health and Welfare. A total of 2,018 subjects aged 10 - 18 years participated in the 2010 - 2011 survey. Among these subjects, those with missing data were excluded. The study population for current growth and socioeconomic characteristics according to BWGA included 1,750 adolescents, and the study population for MS components according to BWGA included 792 adolescents. The criteria for MS in adolescents were based on the International Diabetes Federation consensus (2007).
Results: Among the 1,750 adolescents, the prevalence of SGA was 11.4 % (n=193), the prevalence of appropriate for GA (AGA) was 77.7 % (n=1366) and the prevalence of large for GA (LGA) was 10.9 % (n=191). Current height-deviation score (SDS) [SGA=-0.19(0.09), AGA=0.15(0.04), LGA=0.66 (0.09), $P< 0.0001$] and current weight-SDS [SGA=-0.36(0.09), AGA=-0.06(0.04), LGA=0.28(0.08), $P< 0.0001$] were significantly related to BWGA in Korean adolescents. There were no significant differences in age, sex, gestational age, delivery type, maternal age or household income according to BWGA. Of the 792 adolescents, the prevalence of MS was 1.2% (n=9). There were no significant differences in MS components (abdominal obesity, fasting blood sugar, insulin, HOMA-IR, TG, HDL, Systolic BP or diastolic BP) in adolescents according to BWGA.
Conclusion: BWGA is related to current height and weight in Korean adolescents but is not related to MS components.

P1-d2-484 Growth 2

Percutaneous epiphysiodesis is an efficient and safe method to reduce adult height in extremely tall adolescent boys and girls

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Objective: To further determine the efficacy and safety of a surgical method to reduce height in adolescent boys and girls predicted to extreme tall stature in adulthood. This was done by a second analysis in a study that was first published in 2010, now with an additional 14 patients who have reached their final heights in the last two years.
Patients and methods: All 35 tall adolescents (19 girls and 16 boys) in our center subjected to percutaneous epiphysiodesis around the knee between 1998 and 2010 who had reached their final heights by November 2012 were included. At time of surgery mean height in girls was 178.1±3.4 cm and in boys 186.0±6.5 cm. Prior to the operation, all patients had their bone age determined from an X-ray film of the hand using the atlas of Greulich and Pyle and adult height was predicted according to the Bailey and Pinneau tables. Mean predicted adult height was 190.1±3.4 cm in girls and 206.2±5.1 cm in boys.
Results: In girls, the reduction in adult height was 3.5 ±2.1 cm ($p< 0.0001$), corresponding to 35.2±12.4% of their predicted remaining growth. For boys the reduction was 7.2±3.4 cm ($p< 0.0001$), corresponding to 35.5±14.3% of predicted remaining growth. After surgery, the growth of the upper body segment was 7.5±2.0 cm in girls and 11.2±3.0 cm in boys while leg growth was only 0.3±0.9 cm in girls and 1.5±2.0 in boys, which further supports the efficacy of this treatment.
Thirteen patients in total suffered from postoperative pain for up to two weeks. Other reported side effects included an exostosis at the operation site in one patient and another patient had a postoperative subcutaneous infection which did not require antibiotics.
Conclusion: Bilateral percutaneous epiphysiodesis was effective in reducing adult height compared to prediction in both girls and boys with extreme tall stature and no serious side effects were recorded.

P1-d2-485 Growth 2

Short stature and GH deficiency caused by zinc deficiency in a 6-month-old breast-fed infant due to a dominant negative heterozygous G87R mutation in the Zinc Transporter ZnT-2 (SLC30A2) in the mother

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Background: Zinc (Zn^{2+}) is essential for normal growth and development in infants. Zinc exists in a high concentration in breast milk, especially in the first 3 months. Zinc deficiency in breast-fed infants has frequently been reported. Until recently it was not known why some otherwise healthy and normal nourished mothers may present with low zinc levels in breast milk causing various abnormalities in the baby including growth arrest.
Case description: An otherwise healthy, exclusively breast-fed 6 months old infant presented with a 3 weeks history of increasing skin problems, abdominal cramps and diarrhoea with no obvious malnutrition. The skin lesions appeared like an acrodermatitis enteropathica and serum revealed a significantly low zinc level (2.3 µmol/L; normal values 9-12 µmol/L). Auxologically, a stunted growth (IGF-I and IGF-BP3 levels at -2.3 SDS, -2.5 SDS respectively) and a failure to thrive became obvious starting at the age of 3 months. Serum zinc level of the mother was normal (12.2 µmol/L; 11-18 µmol/L). Zinc concentration in mother's breast milk was 0.12 mg/kg (1.8 µmol/kg),

which was significantly lower than values reported in the literature (0.46 ± 0.26 mg/kg). Genetic investigations revealed a heterozygous G87R mutation in *the zinc transporter* gene, ZnT-2 (SLC30A2). After oral zinc supplementation all the clinical symptoms disappeared and the child presented a catch-up-growth.
Conclusion: Own histochemical analyses of the anterior pituitary gland in mice indicate that Zn^{2+} is present in high concentrations in the Golgi complex and GH-containing secretory granules. Therefore a sufficient Zn^{2+} concentration in the infant is of crucial importance for GH secretion and, thus, normal growth and development.

P1-d2-486 Growth 2

Extending WHO weight-for-age reference curves to older children: a CPEG initiative

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Background: WHO standard curves for infants are based on their prospective Multicenter Growth Reference Study (MGRS). WHO also published reference curves for children 5-19y based on 'core data' from the National Center for Health Statistics (NCHS), collected from 1963-75 on 22,917 US children. These were merged with cross-sectional data from the MGRS (n~8000, 18-71mo) to smooth the transition at age 5. WHO excluded 3% of the NCHS population with weights-for-height < 0.135^{th} or > 97.7^{th} centiles, resulting in a better match to adult definitions of overweight and obesity. Of concern to some clinicians, WHO curves omit weight-for-age beyond 10y to promote the use of BMI.
Objective: To extend WHO weight-for-age curves to ages 10-19y through strict application of WHO exclusion criteria and curve fitting methods to generate the Canadian Pediatric Endocrine Group/CPEG Growth Charts.
Methods: Although raw MRGS data are not in the public domain, NCHS data were kindly provided by the WHO. Based on WHO exclusion criteria, 314 girls and 312 boys were omitted before generating smoothed centiles with the Box-Cox power exponential model in R-GAMLSS.
Results: Table 1 shows the mean absolute discrepancy (MAD) in kg between monthly WHO and re-analyzed NCHS weight-for-age centiles at 5-10y. Percent below is the proportion of NCHS data points below the smoothed weight centile curves for ages 5-19y.

Smoothed Centiles	MAD Boys	MAD Girls	% below (Boys)	% below (Girls)
3	0.12±0.07	0.20±0.11	2.9	2.9
25	0.05±0.03	0.07±0.05	24.5	25.1
50	0.02±0.02	0.17±0.07	50.3	50.1
75	0.08±0.06	0.37±0.18	75.6	75.5
97	0.37±0.21	1.18±0.91	96.8	96.7

[Mean absolute discrepancy (MAD 5-10y, kg+SD)]

Conclusions: CPEG growth charts complement existing WHO reference curves by extending weight-for-age to older children (10-19y). In addition to a more familiar choice of centiles (3,10,25,50,75,90,97), increased granularity in the normal range permits timely identification of aberrant growth.

P1-d2-487 Growth 2

Severity of the disease negatively influences growth in children suffering from homozygous SS sickle-cell disease: results of a single center study

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Background: Growth retardation (GR) and delayed puberty are observed in sickle-cell disease (SCD) due to chronic anemia, inflammation and under nutrition.
Objectives: To assess growth and factors affecting growth in SCD patients.
Methods and patients: Inclusion criteria (IC) were: homozygous sickle-cell (SS) disease diagnosed by neonatal screening, chronological age above 3 years, at least 3 height measurements during the follow-up (FU). GR was defined as a height (H) SD< -2 or/and a loss of height ≥1 SD during the FU. Among the cohort of 518 SCD patients followed in Robert Debré Hospital from 1992 to 2007, 298 patients (150 boys) met the IC. Median duration of FU was 4.5 years (2.7- 6.9) during which 1703 biological tests were performed. Median CA at the first evaluation was 6.8 months (3.5-14). Median Hgb levels were 8.4 g/dl (7.6-9.3), HgbF levels: 18% (11-29) and leucocytes counts: $12.10^3/mm^3$ (9.5-15.3).
Results: 45% patients (n=134) had GR (HSD< -2 or loss of HSD ≥1), HSD< -2 was reported in only 2.3% patients (n=7). GR occurred mainly before 5 years of age (68.6%patients), without any gender differences. Using multivariate analysis, we found 3 statistically significant factors linked to GR: infections (relative risk: 1.15, IC95%:1.1-1.2, p< 0.0001), transfusion therapy (RR: 0.34, IC95%:0.15-0.77, p=0.01), HgbF levels (RR: 0.86, IC95%:0.81-0.92, p< 0.0001).
Conclusion: 45% SCD patients experienced growth disturbances during the course of the disease. Infections negatively impact growth possibly through inflammation and inadequate caloric intakes. Greater Hgb and HbgF levels (via transfusion and hydroxyurea therapies) are associated with a better growth status.

P1-d2-488 Growth 2

Study on the role of amino-terminal propeptide of C-type natriuretic peptide (NTproCNP) in children with short stature

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Background: C-type natriuretic peptide (CNP) is a paracrine growth factor which is produced in the growth plate chondrocyte that plays an important role in regulating linear growth.
Objective and hypotheses: The purpose of this study was to investigate the role of CNP (NTpro CNP) in children with short stature due to various causes in linear growth.
Methods: The study involved 193 children (118 boys and 75 girls), aged 11.46 ±1.88 yrs (7.38-15.29 yrs). Among theses children 33 patients was diagnosed as growth hormone deficiency. Plasma NTproCNP level were measured using commercial kit by ELISA method.
Results: The patients was divide into three groups according to the age as 7-9yr, 10-12 yr and 13-15 yr. The mean plasma NTproCNP levels were 7.09±1.79pmol/L, 9.27±2.68pmol/L, 9.37±2.48pmol/L in boys respectively and 8.18±2.19pmol/L, 8.51±2.16pmol/L, 8.99±1.71pmol/L in girls, respectively. The mean plasma NTproCNP levels in boys, levels from 7-9 yrs were lower than those of 10-13 yr, 13-15yr with statistic significance, respectively (P=0.0041, P=0.0052). The distribution of plasma NTproCNP level show very similar patterns with those of serum IGF-I levels in whole patients regardless of gender. There were no significant differences of mean plasma NTproCNP levels between GHD patients group and non-GHD patients group. Thirty patients were treated by growth hormone with average duration of 0.51±0.08 yrs, among these nine patients were GHD. After GH treatment, the mean plasma NTproCNP level was increased compared with

that of before treatment but there was no statistic significance. The ⊿tNT-proCNP shows a significant correlations only with ⊿t IGF-I in the GH treating children (P=0.0035).
Conclusions: There are significant correlations between plasma NTproCNP level and height, serum IGF-I level in children with short stature. But there were no significant differences of plasma mean NTproCNP levels in children with short stature according to the etiology.

P1-d2-489 Growth 2

Endocrine and genetic assessment of a girl with Weaver syndrome

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Background: Weaver syndrome is an overgrowth disorder characterized by distinct facial features, advanced bone age, intellectual disability, metaphyseal flaring of the long bones and camptodactyly. In 2011 Tatton-Brown et al. found that germline mutations in the oncogene *EZH2* cause Weaver syndrome and increased human height.
Objective: We undertook endocrine and molecular genetic analyses in a Japanese girl with tall stature in whom the diagnosis of Weaver syndrome was suspected.
Case report: The patient was delivered at 38 weeks gestation with a length of 54.2 cm (plus 2.6 SD), a weight of 3805 g (plus 2.5 SD) and an occipitofrontal circumference of 35.0 cm (plus 1.1 SD). She had macrocephaly, broad forehead, ocular hypertelorism, long prominent philtrum and small dimpled chin. Large hands and feet, camptodactyly of hands, soft loose skin, and low-pitched hoarse cry were also noticed. In the first few years she developed hypertonia and flexion contractures. Despite being prescribed an oral estrogen replacement therapy for growth suppression from 10 to 12 years old, her height was 192.1 cm (plus 6.6 SD) when she was 15 years and 9 months old. She had moderate intellectual disability.
Methods and results: No excess of growth hormone and NT-proCNP (c-type natriuretic peptide) was detected. Neither deletion nor point mutation of the nuclear receptor SET-domain-containing protein 1 (*NSD1*) gene, which is responsible for Sotos syndrome, was identified. Array CGH (comparative genomic hybridization) identified no causative abnormality. However, analysis of the *EZH2* gene found a de novo mutation (c.2017A>T_p.N673Y).
Conclusion: The clinical diagnosis of Weaver syndrome was confirmed in our patient following *EZH2* analyses allowing more accurate counselling for the affected and her family.

P1-d2-490 Growth 2

Accuracy of different GH provocative tests for the diagnosis of GH deficiency in children

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Background: The diagnosis of GH deficiency (GHD) in children and adolescents is based on reduced peak GH response to at least two provocative tests. The Cut-off limits of peak GH (CpGH) is arbitrarily set between 7-10 µg/l.
Objective: This study evaluated the diagnostic accuracy of different CpGH in response to Clonidine (Clo), Insulin Tolerance Test (ITT), Arginine (Arg) and Spontaneous Sleep (SS) in children with short stature.
Patients and methods: We studied 978 patients (609 M, 369 F; aged 0.8-18 yr) who underwent GH secretion studies for short stature. GHD was diagnosed in patients with two GH peaks < 10 µg/L (244 GHD, 645 controls). GH and IGF-I, dosed in all patients, were measured by chemiluminescence assay. ROC analysis (RA) and Likelihood Ratio (LR) were used to evaluate the diagnostic accuracy of the tests. RA and LR were repeated also assuming as CpGH of 7 µg/L (135 GHD; 843 controls).
Results: RA showed that a CpGH of 7 µg/L has better diagnostic accuracy than a CpGH of 10 µg/L: Arg (AUC=0.9, Sens=100%, Spec=72.6%, LR+=3.65 vs AUC=0.85, Sens=100%, Spec=61.5%, LR+=2.59), ITT (AUC=0.89, Sens=100%, Spec=67%, LR+=3.03, vs AUC=0.86, Sens=100%, Spec=56.5%, LR+=2.3), Clo (AUC=0.98, Sens=100%, Spec=96.1%, LR+=25.35, vs AUC=0.98, Sens=100%, Spec=94.4%, LR+=17.74) and SS (AUC=0.96, Sens=100%, Spec=89.5%, LR+=9.52, vs AUC=0.94, Sens=100%, Spec=85.5%, LR+=6.91).
IGF-I has low accuracy in the diagnosis of GHD using both cut-offs (AUC=0.71 with 7 µg/L, AUC=0.66 with 10 µg/l).
Conclusions: The use of peak GH cut-off limit of 7 µg/l improves the diagnostic accuracy of all GH provocative tests studied (Arg, ITT, Clo and SS). Clo showed the best accuracy at both cut-offs. IGF-I is characterized by low diagnostic accuracy. These results suggest that a CpGH of 7 µg/L for the diagnosis of GHD might be more accurate.

P1-d1-491 Perinatal and Neonatal Endocrinology 1

Alterations in protein expression in small for gestational age infants born at term

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Background: Most neonates (NN) classed as small for their gestational age (SGA) show subsequent catch-up growth, but many still display long-term comorbidities, including a number of pathologies that influence growth, metabolism and/or the development of other disorders. Identification of the protein alterations displayed SGA NNs may help to identify biomarkers for this physiopathology.
Objetive and hypotheses: To identify changes in the serum proteome in SGA neonates born at term vs adequate for gestional age (AGA) neonates born at term.
Method: The study comprised 30 NNs born at term (15 SGA and 15 AGA), free of genetic abnormalities, malformations and congenital infections. Serum samples were obtained at birth, at one week and at one month of age. Major proteins were equalised using the Proteominer kit (Bio-Rad®). Resulting samples were analysed by two-dimensional polyacrylamide gel electrophoresis (2-DE-PAGE), which yielded the characteristic spot pattern. Quantitative densitometry and statistical analyses were performed using the Proteomweaver v 4.0 software package (Bio-Rad®), and Student's t test were used to check for differences in protein expression between SGA and AGA.
Results: Intergroup differences were found for 6 proteins:
1) One was found only in SGA NNs for all three measurements. The other 5 were missing in SGA NNs for at least one measurement:
2) One was expressed only in AGA NNs for all three measurements.
3,4) Two were expressed in AGA NNs only at birth.
5) One was displayed at a late stage in both groups.
6) Finally, one was found in the AGA group for all three measurements, but in the SGA group only at birth.
Conclusions: Significant intergroup differences were observed in protein expression between the two groups of NNs at all three measurements. Proteome analysis may help to identify biomarkers which could prove useful in the prevention and treatment of complications linked to this condition.

P1-d1-492 Perinatal and Neonatal Endocrinology 1

Higher expression of Klotho/FGF system in placentas from small for gestational age newborns: relation with birth growth and length

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Background: The fibroblast growth factor (FGF) subfamily of ligands, FGF19, FGF21, and FGF23, function as hormones that regulate fatty acid, glucose, and phosphate metabolism in target organs by activating FGF receptors (FGFR1-4). Klotho homologous single-pass transmembrane proteins that bind to FGFRs are required for the metabolic activity of FGF23.
Objective and hypotheses: To determine the placental Klotho, FGF23, FGFR1 and FGFR2 expression in full term pregnancies from small (SGA) appropriate (AGA) and large for gestational age (LGA) newborns.
Methods: We studied 28 cases of idiopathic SGA (birth weight (BW) = -1.73±0.08 SDS), 30 AGA
(BW= 0.06±0.13 SDS) and 28 LGA (BW= 2.30±0.12 SDS) full term pregnancies. Placental mRNA expression was determined by RT-PCR in the chorionic (CP) and basal (BP) plate of the placentas, and normalized using 18S rRNA expression. Results are expressed as mean arbitrary units (AU) ± SEM.
Results:

		SGA	AGA	LGA
Klotho mRNA/18 S rRNA (AU)	CP	1.13±0.21*	0.61±0.27	0.72±0.11
	BP	1.12±0.19**	0.78±0.12	0.69±0.10
FGF23 mRNA/18S rRNA (AU)	CP	0.22±0.03	0.17±0.03	0.20±0.03
	BP	0.23±0.04	0.17±0.02	0.21±0.03
FGFR1 mRNA/ 18S rRNA(AU)	CP	0.35±0.07***	0.21±0.03	0.27±0.06
	BP	0.19±0.02	0.16±0.03	0.18±0.03
FGFR2 mRNA/ 18S rRNA (AU)	CP	1.07±0.16***	0.66±0.11	0.85±0.12
	BP	1.03±0.15***	0.68±0.10	0.83±0.12

[Table 1]
* SGA vs LGA; **SGA vs LGA; *** SGAvs AGA (ANOVA, p< 0.05
We observed a negative Spearman correlation between Klotho mRNA vs birth weight
(r= - 0.27, p=0.014) and birth length (r= - 0.23, p= 0.038).

Conclusions: The higher Klotho and FGFR1/2 expression observed in the SGA compared with AGA placentas, and the inverse correlation with birth weight and length, suggest that this system may be influencing fetal growth in humans.

P1-d1-493 Perinatal and Neonatal Endocrinology 1

Following the Canadian Pediatric Society and the American Academy of Pediatrics guidelines for the management of neonatal hypoglycaemia will miss some neonates with transient perinatal stress hyperinsulinism

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Background: Transitional hypoglycemia occurs in approximately 30% of newborns and pathological hypoglycemia in < 1%. It is very important to differentiate the pathological forms as unlike transitional hypoglycemia, they may cause brain damage and death. Perinatal Stress hyperinsulinism (PSHI) is the most common form of pathological hypoglycemia that persists beyond the first days of life. Current recommendations from the Canadian Pediatric Society (CPS) and American Academy of Pediatrics (AAP) attempt to guide the physician in the management of neonatal hypoglycemia.
Objective and hypotheses: To determine if following the CPS and AAP guidelines will identify all patients with PSHI.
Methods: This is a retrospective chart review of 22 patients with PSHI.
Results: We evaluated 22 patients, of whom 13 were male, 12 AGA (10 term), 9 IUGR (4 term) and 1 term LGA. The final diagnosis was PSHI lasting >7 days in 19 (86%). 19 of 22 presented with hypoglycemia in < 24 hours of age and the remainder at 2 and 3 days. All required IV fluid at some point to control glucose levels. The diagnostic test was performed at mean age of 17 days (2-54). Of the 19 patients with PSHI, 6 were on iv fluids at the time of diagnosis and 13 had a 9 hour fast because they successfully weaned from IV fluids. Hypoglycemia < 50mg/dl occurred at < 3 h in 4, at 3h in 4, at > 3h in 5. The glucose level at 6 hours in the one fast that required 9 hours was 54. In all 5 normal infants the 9 hour glucose was >74 mg/dl, and the lowest glucose at the 6 hours time point was 62 mg/dl.
Conclusions: Following the CPS and the AAP guidelines for the management of neonatal hypoglycemia will miss 26% of neonates with PSHI. Screening criteria should include infants with perinatal stress, C-section delivery and maternal hypertension. Prior to discharge all patients who needed IV glucose to treat hypoglycemia should have a 6 hour fast performed and if the 6h glucose is > 65mg/dl the patient may be safely discharged.

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Hypophosphataemia in small for gestational age extremely low birth weight infants receiving parenteral nutrition in the first week after birth

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Background: To prevent the risk of delays in growth and neurodevelopment and the risk of extrauterine growth restriction (EUGR), aggressive nutrition for preterm infants is becoming common throughout the world.
Objective and hypotheses: In our department, we observed that small for gestational age (SGA) extremely low birth weight infants (ELBWI) who received aggressive nutrition became hypophosphatemic and hypercalcemic in the early neonatal period. This study was undertaken in order to investigate the observed hypophosphatemia and hypercalcemia in SGA ELBWI.
Methods: A retrospective review of 58 SGA and appropriate for gestational age (AGA) ELBWI (mean weight 750 g, gestational age (GA) 23-29 weeks) who received aggressive nutrition in our unit over the last 2 years was conducted. Serum Ca and PO_4 concentrations on days 1 and 8 after birth were examined for associations with parameters including birth height and birth weight standard deviation (SD) score, parental amino acid (AA) administration, total AA administration, total energy intake, and PO_4 and Ca intakes from day 1 to day 7 after birth. Results were compared between SGA and AGA ELBWI.
Results: Lower birth weight standard deviation (SD) scores were correlated with hypophosphatemia and hypercalcemia in SGA ELBWI on day 8. Higher parenteral amino acid (AA) administration was correlated with hypophosphatemia on day 8. SGA ELBWI exhibited lower serum PO_4 concentrations compared to appropriate for gestational age (AGA) ELBWI on day 8.
Conclusions: To the best of our knowledge, this is the first study to report that parental nutrition in the first 7 days after birth for treatment of SGA ELBWIs was correlated with hypophosphatemia and hypercalcemia, perhaps due to overnutrition. It is important to determine an ideal nutrition protocol for treatment of SGA ELBWIs with the awareness that such infants were most likely undernourished in utero.

P1-d1-495 Perinatal and Neonatal Endocrinology 1

Differences in IR/IRS-1/AKT/mTOR protein contents and their response to IGF-I in human term and preterm placentas

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Background: The human placenta expresses the mRNA and protein for IGF-I, Insulin receptor (IR) and IGF-IR and their intracellular signal components (IRS-1, AKT and mTOR).
Objective and hypotheses: To study the protein contents of IR, IRS-1, AKT and mTOR in human term (37-41 weeks of gestation, WG) and preterm SGA and AGA placentas (32-36 WG). We also studied the effects of IGF-I on activation of IR, IRS-1, AKT and mTOR in these placentas.
Methods: We collected placentas from 8 SGA (birth weight (BW) = -1.81 ± 0.20 SDS), 8 AGA (BW= -0.40 ± 0.29 SDS) 8 PT-SGA (BW= -2.32 ± 0.26 SDS) and PT-AGA (BW= 0.72 ± 0.14 SDS) newborns. The effect of IGF-I was determined by stimulating placental explants with recombinant IGF-I 10-8 M for 5, 15 30 and 60 minutes. The total contents and phosphorylated IR, IRS-1, AKT and mTOR were determined by Western Blot and normalized by actin, or with the respective total content. The effect of IGF-I is shown as area under the curve (AUC) in the Table as mean ± SEM: The differences were studied by Mann-Whitney test.
Results:

	SGA	AGA	PT-SGA	PT-AGA
Total IR/actin	1.38±0.35	1.87±0.98#	0.78±0.23*	0.27±0.06
Total IRS-1/actin	1.35±0.44*	0.30±0.11	0.52±0.35	0.15±0.05
Total AKT/actin	3.44±0.56*,#	2.20±0.31#	1.00±0.38	0.74±0.37
Total mTOR/actin	3.89±0.89*	0.75±0.19	1.99±0.98	1.29±0.40
AUC IR	102.5±9.7*,#	56.3±6.3#	41.5±3.5*	17.1±5.7
AUC IRS-1	26.1±1.9#	21.7±1.8#	16.3±1.2*	8.6±1.6
AUC AKT	29.5±2.2*,#	21.9±1.7	18.6±3.2	19.7±2.9
AUC mTOR	75.2±8.1	80.1±7.7#	57.8±2.5*	26.1±9.7

[Table 1]
* p< 0.05 SGA vs AGA or PT-SGA vs PT-AGA
# p< 0.05 SGA vs PT-SGA or AGA vs PT-AGA

Conclusions: The higher contents of IR, IRS-1, AKT and mTOR in SGA and PT-SGA placentas compared with AGA and PT-AGA placentas respectively, and the higher response to IGF-I of these placentas, suggest that these placental signal transduction proteins may influence fetal growth. (FONDECYT 111-0240).

P1-d1-496 Perinatal and Neonatal Endocrinology 1

Identifying the growth-restricted neonate

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Background: In daily practice the diagnosis of the growth-restricted (IUGR) neonates is based on birth weight (BW), despite wide awareness that low-birth-weight babies are not necessarily IUGR and vice versa.
Objective and hypotheses: To assess the value of the combined use of common indicators of nutritional status in the identification of IUGR babies.
Methods: Four anthropometric indices (i.e., BW, chest circumference, mid-arm circumference, ponderal index) and the nutritional status, evaluated through Clinical Assessment of Nutritional Status (CANS) score, of 166 newborns ≥35 weeks gestational age (GA) were assessed. The placental weight was recorded and the cord blood insulin-like growth factor I (IGF-I) and IGF binding protein 3 (IGFBP-3) levels were assayed. Three dichotomous variables were developed: BW25, BW2500 and GR. In BW25 the babies were allocated into two groups by having a BW either ≤ or > 25th centile for GA. In BW2500 the BW cut-off level was set at 2500 g. GR included babies having either 2 (or more) out of the 4 anthropometric indices ≤25th centile for GA or all 4 anthropometric indices > 25th centile for GA. For statistical evaluation multiple linear regression analyses were performed.
Results: BW25 explained 12.10%, 11.78%, and 30.07% of the variation of the IGF-I, IGFBP-3 levels and of the placental weight, respectively. The corresponding associations of BW2500 with the above three dependent variables were 8.03%, 11.17% and 9.68%, respectively. The variable GR along with CANS score explained 23.88%, 22.53% and 36.47% of the variation of the three dependent variables, respectively. All the relationships were highly significant. The association of BW, dichotomized at the 10th centile for GA, with the three dependent variables was not stronger than that of the variable BW25.
Conclusions: Compared to BW in isolated use, the combination of simple indicators of nutritional status offers a better approach for identifying IUGR babies.

P1-d1-497 Perinatal and Neonatal Endocrinology 1

Adiponectin and serum leptin levels of large for gestational age (LGA) newborns with a weight gain more than 1.0 Kg during the first month of life

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Background: To determine the dynamic of the levels of adiponectin and leptin of LGA newborns during the first month of life and to establish the relationship of these parameters with the rate of physical development of infants.
Objective and hypotheses: 77 term infants, large for gestational age (birth weight 4270.0 ± 0.22 g) were divided in to two groups according to the weight gain during the first month of life: more than 1 kg (n = 34) - 1st group, less than 1 kg (n = 43) 2nd group. Body weight (m), body mass index (BMI), ponderal index (PI) at birth in both groups were similar (p = 0.337 - 0.455).
Methods: Ante- and intranatal anamesis were analyzed, clinical and laboratory examination, levels of adiponectin («A») and leptin («L») at 1, 6 and 30 days of life were perfomed. Adipocytocines using immunosorbent assay: DRG Leptin (Sandwich) ELISA (EIA-2395) and DRG Adiponectin (human) ELISA (EIA-4177) were determined. Statistical data processing was performed using Excel 2007, SPSS 17 (p< 0.05 was defined as significant).
Results: A distinction of anthropometric indices during the 1st month of life (body weight (p = 0.0001), BMI (p = 0.0001), PI (p = 0.001)) between two groups were revealed. Weight gain during this period in group 1 was 1.1 ± 0.21 (kg) in the 2 - 0.7 ± 0.23 (kg) (p = 0.0001). Infants were on different types of feeding: breast milk & formula (χ^2=1.98, p=0.159). Significant differences in content of serum «A» level in infants we have not found (p = 0.404-0.933), but correlation between PI and «A» level at 1 month (r = -0.36, p = 0.049) was defined. The concentration of «L» in children 1st group was significantly (p = 0.001) higher (121.6±54.8 ng/ml) than in group 2 (73.3±45.7ng/ml).
Conclusions: Our findings: hyperleptinemia and negative correlation link between PI and adiponectin levels in LGA newborns with a weight gain more than 1.0 kg during the first month of life, can be used as a predictor of unfavorable metabolic-being in the future.

Relation of gestational age to ratios of serum insulin-like growth factor-II to serum Insulin-like growth factor binding protein-3 in the not-life-threatened newborn: relevance of the proportion between estimated birth brain weight and birth body weight beyond the presence of caesarean section and of a small birth body weight for gestational age

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Background: We evidenced inverse relations of gestational age at birth in complete weeks (GA) with blood serum ratios of Insulin-like Growth Factor (IGF)-II (IG2) to IGF Binding Protein 3 (IB3)(IG2/IB3) in the human newborn (NWB).
Objective and hypotheses: We studied the role of estimated birth brain weight (BRW) to birth body weight (BW) ratio (BBR) in NWB relations of GA to IG2/IB3 independently of Caesarean Section (CS) and of a BW< 10.th centile for GA (SGA).
Methods: 78 NWBs,
1) with complete data for gender (SEX), GA, BW, birth head circumference (HC), SGA, IG2 and IB3 measured by RIA in uM/dL at one of the first 5 postnatal (PN) days (x), 5 days after x (y) and 10 days after x (z), and PN age at x in days (PNA) and
2) without any among life-threatening disease, diabetes mellitus (DM) and mother with DM (males,n=43;GA≤36,n=46,CS,n=52;SGA,n=20;GA range=28-42; BW range=1200-4150gr) were included in the study. IG2/IB3 (IG2 through chronol. corresponding IB3) standardized according to Van der Waerden (IG2/IB3-S) was near-normally distributed. Following McLennan-Lindley, BRW and BBR were calculated by the formulas "$BRW=0.037xHC^{2.57}$" and "BBR=100x(BRW/BW)"(units; BW=gr; HC=cm). Spearman's correlation (SC) and multiple linear regression (MLR) were used (computations; male SEX, SGA and CS; condition present=1, otherwise=0).
Results: Rho of BBR SCs with IG2/IB3 at x, y and z were resp. .37, .42 and .44 (p=.0008-.0001). Tab.1 shows MLR models bearing IG2/IB3-Sx-y-z as outcome and as predictors either
1) GA,SEX,CS,SGA and PNA (Tab.1A) or
2) GA,SEX,CS,SGA,BBR and PNA (Tab.1B) as GA partial correlation coefficient (r)-t-p and model R2-F-p.

A)	vs.	IG2/ IB3-Sx	IG2/ IB3-Sy	IG2/ IB3-Sz	B)	vs.	IG2/ IB3-Sx	IG2/ IB3-Sy	IG2/ IB3-Sz
GA	r	-.349c	-.352c	-.389d	GA	r	-.193ns	-.132ns	-.128ns
	t	-3.157	-3.188	-3.680		t	-1.660	-1.119	-1.090
	R2/F	.275/ 5.466d	.208/ 3.783b	.193/ 3.680a		R2/F	.282/ 4.655d	.239/ 3.714b	250/ 3.939c
Signif.:	a, p<.0100;	b, p<.0050;	c, p<.0025;	d, p<.0005;	ns. p not significant.				

[Tab.1]

Conclusions: BBR could be involved in GA relations to IG2/IB3 independently of CS and SGA.

Higher PINP in small-for-gestational-age (SGA) preterm infants is associated with increased growth during the first six months post-term

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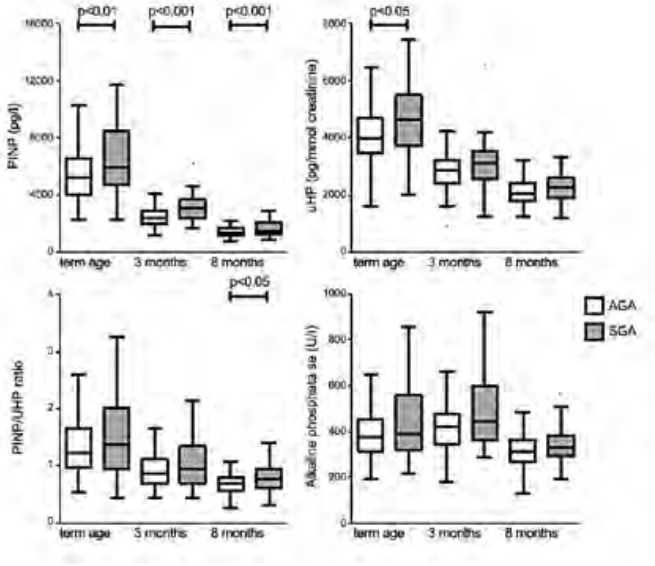
Background: Small-for-gestational-age (SGA) preterm infants have increased growth and lower bone mineral content (BMC) gain compared to appropriate-for-gestational-age (AGA) preterm infants during infancy.
Objective and hypotheses: To study growth and to identify growth-related collagen and bone markers in SGA and AGA preterm infants between term age (40 weeks postmenstrual age) and six months post-term. We hypothesized that growth is positively associated with collagen and bone markers.
Population and methods: At term age, three and six months post-term, weight (g), length (cm), procollagen type I N-terminal peptide (PINP; µg/l), urine helical peptide (UHP; µg/mmol creatinine), and alkaline phosphatase (ALP; U/l) were measured in 98 AGA and 33 SGA (weight and/or length at birth < -2 SDS) infants (gestational age (median (interquartile range)): 30.3 (2.0) versus 31.1 (1.6) weeks; 42.9 versus 72.7% boys).
Results: SGA infants had higher PINP and UHP at term age, higher PINP at three months, and higher PINP and PINP/UHP ratio at six months post-term, whereas ALP was similar (Figure 1). PINP and UHP at term age and PINP and PINP/UHP ratio at three months post-term were associated with subsequent weight and length gain until six months post-term.
Conclusions: During the first six months post-term, increased collagen type I synthesis in SGA preterm infants is associated with growth, suggesting that PINP may be a promising growth marker in preterm infants. Increased collagen type I synthesis is not accompanied by increased bone mineralization, as suggested by similar ALP, which may explain the lower BMC in SGA preterm infants.



[Figure 1. PINP, UHP, PINP/UHP ratio, and ALP]

P1-d1-500 Perinatal and Neonatal Endocrinology 1

Body mass index and ponderal index references for newborn at 28-42 weeks gestation

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Background: Body mass index (BMI) at birth and first 3 month are the best predictors of overweight at age 5-7 years. Malnutrition defined as a BMI below the 5th percentile is also associated with many health problems.
Ponderal index (PI) is used to diagnose abnormal fetal growth. A high or low PI can be possible indicator for diseases such as obesity, hypertension, and coronary heart disease in the future.
Objective and hypotheses: The aim of this study is to develop BMI and PI references for infants born at 28-42 weeks gestation.
Methods: Data were collected from neonatal records of perinatology services of eleven hospitals during two years. The anthropometry of a total of 6500 singleton live births born between 28 and 42 weeks of gestation were recorded. Means and standard deviations were calculated, and percentiles for each gender and gestational week were produced using the LMS program.
Results: Gestational age and gender specific 5th, 10th, 15th, 25th, 50th, 75th, 85th, 90th and 95th percentile values were produced. Comparison of the 5th, 50th and 95th percentile values, BMI values of girls in the 5th and 50th percentile values were lower then boys while 95th percentile didn't have a significant difference. PI values of 10%, 50%, and 90% have been observed to be similar between boys and girls. The proportion of newborn with ponderal index < the 10th percentile and ponderal index > the 90th percentile were 8.0% and 8.4% respectively.
Conclusion: This experiment results have concluded that BMI and PI percentiles should be added to the weight, length and head circumference growth curves as a routine intrauterine growth assessment at birth. Additionally these references will be of use in clinical practice and for research.

P1-d1-501 Perinatal and Neonatal Endocrinology 1

Concurrent argininosuccinic aciduria in a patient with Russell-Silver syndrome caused by maternal uniparental isodisomy of chromosome 7

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Objective: To assess the etiology of a patient with concurrent Russell-Silver syndrome and argininosuccinic aciduria.
Design, case report and setting: Medical genetics diagnostic unit in a university hospital.
Patient: A 1-year-old girl was referred to our hospital with symptoms of failure to thrive, hepatomegaly and intermittent vomiting. Russell-Silver syndrome was suspected due to characteristic of facial appearance and intrauterine growth retardation. Genetic study of Russell-Silver syndrome in this girl confirmed that she has maternal uniparental isodisomy of chromosome 7. However, the causes of hepatomegaly and persistent abnormal liver function remained unanswered. Two months later, sudden onset of lethargy, seizure attack and elevated serum ammonia (545mcg/dl) was noted. The serum amino acid analysis revealed an elevated argininosuccinate. The mutational analysis of ASL gene revealed that this girl is homozygous for c.2T>A, p.M1K, homozygous mutation. Her mother is heterozygous for this p.M1K mutation, but this mutation could not be identified in her father.
Result(s): This result suggests that not only Russell-Silver syndrome but also argininosuccinic aciduria in this girl was caused by maternal uniparental isodisomy of chromosome 7.
Conclusion: This is the first case report of the concurrence with Russell-Silver syndrome and argininosuccinic aciduria in a patient and discloses an alternate mechanism whereby argininosuccinic aciduria can be derived from a single parent.

P1-d1-502 Perinatal and Neonatal Endocrinology 1

Catch-up growth by itself following fetal growth restriction is an adaptive compensation and does not induce metabolic changes until three years of age

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Background: Early post-natal catch-up growth (CUG) following intra-uterine growth retardation is regarded as a risk factor for later metabolic complications.
Objective: To determine if CUG following fetal growth restriction (FGR+) induces any metabolic changes at the age of 3 years.
Methods: 93 infants were prospectively followed from mid-gestation to 3 years of age (CASyMIR cohort). Fetal growth velocity (FGV) was measured from ultrasound measurements and calculated as the change in customized percentiles of estimated fetal weight. FGR was defined as the loss of more than 25 percentiles between 22 weeks of gestational and birth. Annual metabolic and anthropometric evaluation was performed from birth till the age of 3 years.
Results: 32 infants had experienced previous FGR (FGR+) without having significantly lower birth weight compared to 61 FGR- infants (-1.1±0.7 vs. -0.8±1.1 z-score; p=0.14). However, ponderal index and fat mass were lower at birth (25.2±2.4 vs. 26.3±2.5 kg/m3; p=0.03: 13.1±4.2 vs. 16.1±4.8%; p=0,03). At 1 yr of age CUG lead to the restoration of BMI (0.2±0.7 vs. -0.3±1.4 z-score; p=0.69) and of fat mass (18.2±3.8 vs. 18±4.5%; p=0.85). Until the age of 3, BMI (0.3±1.2 vs.-0.4±1 z-score; p=0.51) and fat mass (18.8±4 vs. 19.9±6.9%; p=0.36 at 2 yr and 19.8±4.5 vs. 19±4.4%; p=0.49 at 3yr) remained similar between FGR+ and FGR-, without any significant differences in insulin (2.1±1,6 vs.1.7±1.1 mUI/l; p=0.22 at 2yr and 2.4±1.3 vs. 2.4±2.8 mUI/l; p=0.85 at 3yr) and leptin (4.2±1,8 vs. 3.6±1.4 ng/ml; p=0.26 at 2yr and 4.1±1.8 vs. 3.9±1.1 ng/ml; p=0.59 at 3yr) levels and calories intakes (1034.4±212.4 vs. 1080.3±237 Kcal; p=0.38 at 2yr and 1173.1±258.7 vs. 1180.8±243.2 Kcal; p=0.9 at 3yr).
Conclusions: Early catch-up growth, which preserves height and weight without detectable excess of fat mass or in calorie intake does not cause metabolic abnormalities in 3 years old children and appears to be an adaptive correction following fetal growth restriction.

P1-d1-503 Pituitary and Neuroendocrinology 1

Genotypic classification of Wolfram syndrome patients: insights into the natural history of the disease and correlation with phenotype

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Background: Wolfram Syndrome is a degenerative recessive rare disease with an onset in childhood. Also known as DIDMOAD for the four main symptoms (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness), it is caused by mutations in *WFS1* or *CISD2* genes. More than 200 different variations in *WFS1* have been described in Wolfram Syndrome patients and no common mutation has been determined.
Objective: To further elucidate the role of *WFS1* mutations on disease progression, to establish a clear genotype-phenotype correlation and to update

the natural history of the disease.
Methods: The study analyzed the clinical and genetic data of 412 Wolfram Syndrome patients published in the last 15 years.
Results: Results indicate that i) 15% of published patients do not fulfill current inclusion criterion so a new one is proposed; ii) genotypic prevalence differences may exist among countries; iii) the first two clinical features of the syndrome might not be diabetes mellitus and optic atrophy; iv) identified mutations distribute non-uniformly on the protein ; v) the age at onset of diabetes mellitus, hearing defects and diabetes insipidus may depend on the patient's genotypic class; vi) a progression rate for the disease could be estimated that might depend on genotypic class.
Conclusions:
i) a new inclusion criterion that comprises most Wolfram Syndrome patients is needed,
ii) there are two additional regions important for protein function,
iii) patient's genotypic class may determine disease progression and age at onset of the different symptoms.
The conclusions raised could be important for patient management and counseling as well as for the development of treatments for Wolfram Syndrome.
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P1-d1-504 Pituitary and Neuroendocrinology 1

Novel mutations in *PAX6* cause congenital hypopituitarism with or without ocular malformation

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Background: Mutations in transcription factors genes, whose expression are regulated spatially and temporally in the pituitary gland, result in congenital hypopituitarism (CH) in humans. The prevalence of CH attributable to these gene mutations appears to be rare and other causative genes for CH remains to be identified. Due to the sporadic occurrence of CH, *de novo* chromosomal rearrangements could be one of the molecular mechanisms participating in its etiology, especially in syndromic CH.
Methods: We enrolled 88 (Syndromic:30 Non-syndromic:58) Japanese CH patients. The inclusion criteria were 1) severe GH deficiency (GH peak <3 ng/mL), and 2) anterior pituitary hypoplasia. In all the patients, mutations in *POU1F1, PROP1, LHX3, LHX4, HESX1, SOX2, SOX3, OTX2*, and *GLI2* have been excluded. We performed an array CGH screen of 30 syndromic CH patients to determine the role of copy number variations in the etiology of CH. We sequenced all coding exons and flanking introns of *PAX6* in all 88 patients. Transcriptional activity of identified *PAX6* variants was evaluated by functional reporter assays, using luciferase reporter constructed by inserting the *PAX6* binding element sequences. We also performed western blotting and subcellular localization analyses.
Results: We identified one heterozygous 350kb deletion of *PAX6* enhancer region in one patient with isolated GH deficiency, cleft palate, and optic disc cupping. We identified a novel *PAX6* mutation, namely p.N116S in one non-syndromic CH patient with isolated GH deficiency. *In vitro* experiments showed that N116S PAX6 resulted in a decrease of luciferase activity, without any dominant-negative effects.
Western blotting, visualization of subcellular localization revealed no significant difference between the wild type and N116S.
Conclusions: For the first time, we show that heterozygous *PAX6* mutations may lead to CH with or without ocular malformation. The frequency of *PAX6* mutations in CH patients was 2.3%.

P1-d1-505 Pituitary and Neuroendocrinology 1

Prevalence of microadenomas in children with isolated growth hormone deficiency and central precocious puberty

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Background: Pituitary microadenomas are extremely rare in childhood and have been occasionally described in children with both Isolated Growth Hormone Deficiency (IGHD) and Central Precocious Puberty (CPP), although they do not seem to play any role in their pathogenesis. Pituitary incidentalomas usually show a benign and non-progressive behavior. To date, clear guidelines on their management have not been established.
Objective and hypotheses: To evaluate the prevalence of microadenomas in IGHD and CPP children and their evolution.
Methods: 388 children (aged 0.5-19.3), 248 with IGHD and 140 with CPP were studied. All patients underwent brain MRI scanning with detailed study of the hypothalamic-pituitary area.
Results: Microadenomas were found in 9 patients (3.6%) of IGHD population, and in 16 patients (11.4%) of CPP subjects (p=0.004). Eight patients with IGHD were followed up for an average time of 3.2 yrs (range 0.7-12.1) with yearly MRI scans: during follow-up microadenomas remained unmodified in 2, increased in volume in 1 and became non-visible in 5 patients. Ten patients with CPP were followed up for an average time of 3.1 yrs (range 0.4-7.5): microadenomas remained unmodified in 3, increased in volume in 1, shrinked in 1, and became non-visible in 5 patients. In the 2 patients with microadenoma enlargement no further clinical and/or endocrine signs occurred. In CPP group, baseline and LHRH stimulated LH and FSH levels, as well as 17-beta-estradiol concentrations, were not significantly different between patients with or without microadenomas.
Conclusions: Our data show a significantly higher prevalence of microadenomas in CPP than IGHD patients. This finding raises the issue of a possible pathophysiological role of microadenoma in CPP. Finally, follow up results indicate that whilst some microadenomas disappear with time, thus raising doubts about the initial neuroimaging interpretation, others enlarge progressively, thus requiring careful and regular MRI scans.

P1-d1-506 Pituitary and Neuroendocrinology 1

Copy number variants in Brazilian patients with congenital hypopituitarism

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Background: The aetiology of congenital hypopituitarism (CH) is unknown in the majority of patients. In our cohort of 200 cases in only 13 patients (6.5%) it was possible to establish the genetic cause. Copy number variants (CNVs) have been implicated as the cause of genetic syndromes with previously unknown aetiology.
Objective: To study the presence of CNVs and its relevance in patients with CH of unknown cause.
Patients and methods: 23 patients with CH with at least one of the following features, consanguinity, family cases, mental retardation, dimorphisms or cerebral malformation were selected for whole-genome array-CGH screening in a customized platform of 180K (Oxford Gene Technologies).
Results: Eight patients (34.7%) presented CNVs, three harbouring heterozygous deletions with sizes ranging from 50 to 105KB and 5 harbouring duplications ranging from 357KB to 1.3MB. In seven patients, the CNVs overlap a genomic imbalance in a CNV database for affected individuals (DECIPHER). UCSC database indicates that several genes are involved with these CNVs:

SEPT3, CENPM, MYO3A e VWA3B are deleted and SDK1, CCDC146, FGL2, PION, EMB, PARP8, FAM176A, MRPL19, C2orf3 e PLD5 are duplicated. One of the patients CNV *[ARR 7Q11.23 (76.590.274-77.003.378)X3]* overlaps with the Williams-Beuren duplication syndrome, until now not associated with hypopituitarism. The eighth patient has a 66 KB deletion *[ARR 2Q11.2 (98.066.783-98.132.990)X1]* not found in the DECIFER and in the database for healthy individuals (DGV).
Conclusions: The CNVs found in 8 out of 23 patients may be associated to CH phenotype. Familial segregation along with gene function and pathways is necessary to establish the real pathogenicity of each CNV.

P1-d1-507 Pituitary and Neuroendocrinology 1

Contribution of *OTX2* mutations in the aetiology of congenital hypopituitarism in a selected cohort of patients: novel changes and functional consequences

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Background: *OTX2* (NM172337.2) is a transcription factor implicated in pituitary, ocular and craniofacial development. In mice, it is expressed in the ventral diencephalon and Rathke's pouch and then restricted to the posterior lobe. More than 30 mutations have been described in humans. The pituitary phenotype, when reported (n=10), ranges from IGHD to CPHD with/without an ectopic posterior pituitary (EPP).
Objective and hypotheses: As *OTX2* mutations have so far been reported in single cases or in heterogeneous series, we aimed to establish the contribution of *OTX2* mutations in the aetiology of congenital hypopituitarism in a well-defined patient cohort and to study their functional consequences.
Methods: We screened 125 patients from national (n=101) and international centres (n=24) with eye abnormalities and at least one pituitary hormone deficiency. 57% of those with available MRI results had an EPP (n=33). Functional assays were performed in HEK293T cells with wild type and mutant *OTX2* constructs; reporters included the *HESX1* promoter and *OTX2* consensus binding sites.
Results: Six heterozygous *OTX2* changes were identified (4.8%). These included chromosomal deletions including *OTX2* (n=2), the previously reported p.S138X in a patient with retinal dystrophy, EPP and GHD, and three novel mutations:
(i) p.C170X in a patient with retinal dystrophy, EPP and GHD
(ii) p.E79X in association with anophthalmia/microphthalmia, EPP and MPHD
(iii) insertion-deletion (p.Ser168Argfs6*) in a patient with microphthalmia, GHD, EPP and abnormal pituitary shape.
Mutations resulted in premature termination or loss of the transactivation domain. Patients were negative for mutations in other genes (*HESX1/SOX3/SOX2/PROKR2*).
Conclusions: Loss of function *OTX2* mutations are common in patients with ocular, retinal and structural pituitary defects. As *OTX2* is involved at multiple levels in hypothalamo-pituitary development, monitoring for evolving endocrinopathies is needed.

P1-d1-508 Pituitary and Neuroendocrinology 1

Diencepephalic syndrome before diagnosis of childhood craniopharyngioma: results of multinational studies on 485 long-term survivors after childhood craniopharyngioma

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Background: Hypothalamic involvement (HI) resulting in severe obesity is known to have major impact on quality of life in craniopharyngioma (CP) patients. HI is also associated with disturbances of satiety regulation leading to a failure to thrive and weight loss known as diencephalic syndrome (DS). The rate of DS and the outcome of CP patients with DS is unknown.
Methods: 485 CP patients have been recruited in HIT-ENDO and KRANIOPHARYNGEOM 2000/2007. 21 CP patients (4.3%) presented with a BMI< -2SD at diagnosis. In 4 of 21 cases low BMI could be explained by prematurity or congenital heart failure. 11 patients presented with DS due to proven hypothalamic involvement (HI). 3 patients presented without HI, in 3 patients HI was not evaluable. We compared weight development since birth at standardized time points (based on a German health survey) in CP presenting DS, normal weight or obesity (BMI>3SD) at the time of diagnosis.
Results: Weight development during early childhood could be analyzed in 9 of 11 DS patients. Decreases in BMI (>-1SD) were detectable in 4 patients within the first year of life, in 2 patients in the second year of life, in 2 patients in the 5th year, one patient was already dystrophic at birth. Accordingly, 7 of 11 patients showed BMI reduction within the first two years of life. During follow-up, DS patients showed a significant postoperative weight gain comparable to patients who presented with normal weight at time of diagnosis resulting in obesity (median BMI +3.98SD) after 8-12 years.
Conclusion: DS is a rare clinical manifestation of CP. In the majority BMI SDS reduction becomes manifest in early childhood, in some cases changes in BMI SDS develop later, but years before other symptoms are obvious. Low BMI at time of diagnosis does not prevent weight gain in CP with DS.

P1-d1-509 Pituitary and Neuroendocrinology 1

Lowered FT4 concentrations after starting growth hormone treatment: unmasking of mild congenital central hypothyroidism?

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Background: After starting growth hormone (GH) treatment for apparent "isolated" growth hormone (GH) deficiency (GHD), the free thyroxine (FT4) concentration sometimes falls. When FT4 becomes too low, treatment with thyroxine (T4) is often started. Although benign explanations have been postulated, several studies have shown reduced growth velocity and even lower quality of life.
Object/hypothesis: We hypothesized that this FT4 fall represents unmasking of (mild) congenital central hypothyroidism (CCH), indicating subtle multiple pituitary hormone deficiency (MPHD) instead of isolated GHD. To substantiate this hypothesis, we compared the neonatal screening T4 concentrations of children with a low FT4 necessitating T4 treatment after starting GH, to the neonatal T4 concentrations of children who did not need T4 treatment.
Methods: All Dutch children who started GH treatment for idiopathic GHD between 2001 and 2011 were contacted via their physicians. After informed consent data from the Dutch Growth Foundation and the neonatal screening were retrieved. In total, 458 children (0-18 years) were included, of whom 369 were diagnosed with "isolated" GHD and 89 with MPHD at start of GH treatment.
Results: Of 369 children with apparent isolated GH deficiency, 27 started T4 treatment within two years after starting GH. In total, 132 neonatal screening

results could be retrieved. Children who started T4 treatment after starting GH had clearly lower T4 concentrations shortly after birth compared to children who did not need T4 treatment (neonatal screening T4 concentration standard deviation scores; -1,3 (n=5) vs. -0,31 (n=127), $p < 0,05$).
Conclusions: The clearly lower neonatal T4 concentrations in children who show a clinically relevant FT4 fall after starting GH later in life, suggests that the hypothalamus-pituitary-thyroid axis of these children was already "different" early in life. Whether this represents central hypothyroidism as part of subtle congenital MPHD remains to be proven.

P1-d1-510 Pituitary and Neuroendocrinology 1

Long-term health outcomes of adults with McCune Albright syndrome

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Background: McCune Albright Syndrome (MAS) is associated with fibrous dysplasia (FD), early puberty and endocrine hyperfunction. Whilst management in childhood generally focuses on treatment of fibrous dysplasia and early puberty, adult management is complicated by increasing deformity secondary to FD, acromegaly, fertility difficulties and possible increased risk for cancers. There are few reports of evolving health problems of adults with MAS.
Objective: To describe health outcomes of adults with MAS (> 18 years).
Methods: Retrospective case note audit of 16 adults (8 males) with MAS. Results reported in median [range].
Results: Median age at diagnosis 6 years [0.1, 28]. Median current age 29 years [20, 46].
(1) Fibrous dysplasia: panostotic (n=4,25%), polyostotic(n=11,69%): monostotic -skull (n=1), *Hypophosphataemia requiring treatment* (n=2),
(3) Major disability due to
a. Consequences of deformity from FD (n=10,62.5%)
b. Nerve root impingement from FD (n=3,18.75%)
c. Extensive facial distortion (n=4,25%)
(4) Previous early puberty 2/8 males, 5/8 females
(5) Thyrotoxicosis (n=3, 18.75%) requiring I^{131}, multinodular goitre (n=4, 25%)
(6) Testicular microlithiasis (4/ 8), *testicular mass (5/8)* benign on biopsy (3/8, 62.5%) *Severe oligospermia* (1), normal spermatogenesis (2/3)
(7) Acromegaly (n=4, 25%) continuing high GH, IGF1 despite medical +/- surgical treatment
(8)Platelet dysfunction: 2/7 (29%)
(9) Upper gastrointestinal polyps (5/7) (71%)
(12) Others
High output cardiac failure(2) (both panostotic)
Aggressive breast carcinoma (1 female aged 41
Myxoma (1) female aged 32 (GNAS mutation +ve in tissue).
Leuokoerythroblastic anaemia(1) Pancreatic cyst (1)
Conclusion: Increasingly severe and catastrophic consequences of extensive involvement of GNAS affected tissues exist in adults with MAS, with important implications for transition to adult care. Long term cancer risk is currently unknown especially in relation to upper GI polyps, breast exposure to early oestrogen and testicular abnormalities.

P1-d1-511 Pituitary and Neuroendocrinology 1

Contribution of *GLI2* mutations to pituitary deficits and delineation of the associated phenotypic spectrum

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Background: GLI2 is a zinc finger transcription factor implicated in the mediation of SHH signaling, expressed early during ventral forebrain and pituitary development. Sofar, only 7 unambiguous *GLI2* mutations have been found in patients with hypopituitarism - essentially combined pituitary hormone deficiency (CPHD) - frequently associated with holoprosencephaly-like malformations and/or polydactyly.
Objective and hypotheses:
i) to assess the prevalence of *GLI2* mutations in patients with CPHD, isolated growth hormone deficiency (IGHD) or diabetes insipidus, associated with a personal or family history of midline defects and/or polydactyly/syndactyly,
ii) to provide a most complete description of the *GLI2*-associated phenotypes.
Methods: All *GLI2* coding exons were sequenced in 126 independent probands.
Results: Nine novel heterozygous variations were identified in 9 independent probands (10 patients). Three are non-ambiguously deleterious: 1 nonsense (Arg264*, in 2 siblings) and 2 frameshift mutations (Gly198Argfs*153, *1587Tyrext*46). Three missense variations (Tyr435Cys, Arg720His, Ser941Arg) are expected to be deleterious: they induce a charge/steric change and involve residues invariant through evolution, located within the first zinc finger or the transactivation domain. Three missense variations (Ala117Thr, Ala1077Val, Asp1435Glu) would require functional assessment to confirm their pathogenicity.
The 7 patients with a deleterious/probably deleterious mutation had IGHD (n=4), CPHD (n=2) or diabetes insipidus (n=1). The extra-pituitary defects were: bilateral cleft lip/palate (n=1), unique central median incisor and choanal atresia (n=1), polydactyly (n=3), syndactyly (n=1), septum pellucidum agenesis (n=1).
Conclusions: In this large series of patients with hypopituitarism, a personal or family history of midline defects and/or digit anomalies, *GLI2* mutations are responsible for at least 5% (6/126) of independent cases, most of them with IGHD.

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Treatment of growth hormone excess in two children with neurofibromatosis type 1 (NF-1) with the long-acting somatostatin analogue lanreotide

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Background: Growth hormone excess can occur in the presence of neurofibromatosis type 1 (NF-1). We present two children with NF-1 related growth hormone excess treated with the long-acting somatostatin analogue lanreotide, which has not been reported before.

Patients: Both patients had genetically confirmed NF-1. They were referred for tall stature and growth acceleration in the absence of precocious puberty.
Case 1: This 4 8/12 male presented with a height of 124.5 cm (3.71 SDS). IGF-1 was elevated at 295 ng/ml (2.21 SDS), IGF-BP3 was 3.39 ng/ml (2.3 SDS). Minimum growth hormone level on OGTT was 1.55 ng/ml. On MRI he had bilateral optic pathway gliomas with a normal pituitary. Treatment with lanreotide was gradually increased from 60 mg to 120 mg s.c. every four weeks to normalize both IGF-1 and IGF-BP3. Height was near normal (2.04 SDS) after 18 months of treatment. There was no progression of the optic pathway glioma.
Case 2: This 3 0/12 female presented with a height of 102.7 cm (1.85 SDS). IGF-1 was elevated at 277 ng/ml (3.23 SDS), IGF-BP3 was 4.81 ng/ml (2.00 SDS). Minimum growth hormone level on OGTT was 5.65 ng/ml. She had undergone resection of a malignant peripheral nerve sheath tumor (MPNST) in the right orbita. Treatment with lanreotide was started at 60 mg s.c. every four weeks normalizing both IGF1 and IGF-BP3 levels. Treatment had to be stopped after 2 months due to significant abdominal pain. During this period the MPNST recurred.
Conclusions: Treatment with lanreotide appears to be effective in normalizing IGF-1 and IGF-BP3 levels in children with NF-1 and growth hormone excess. Side effects included significant abdominal pain in one of our patients without pathological liver function tests or gallbladder abnormalities. It remains unclear whether lowering growth hormone levels decreases the risk of occurrence and progression of NF-1 related tumors.

P1-d2-513 Pituitary and Neuroendocrinology 2

Thyroid hormone transporter expression in the murine anterior pituitary lobe

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Background: Thyroid hormone (TH) transporters are necessary for intracellular uptake of TH. Monocarboxylate transporter 8 (MCT8) is known as a highly specific transporter for TH. Allan-Herndon-Dudley syndrome (AHDS), caused by MCT8 mutations, shows elevated FT_3, decreased FT_4, and slightly elevated TSH levels. In *Mct8*$^{-/-}$ mice, *TRH* mRNA expression in the hypothalamic paraventricular nucleus remains persistently elevated unless supraphysiologic amounts of LT_3 or LT_4 are administered. However, serum TSH levels in AHDS patients decrease with administration of a physiological dose of LT_4. We thus hypothesized that T_4 negatively regulates TSH via TH transporters other than MCT8 in thyrotropes.
Objective and hypothesis: We aimed to determine functional TH transporters in the mouse pituitary by comprehensive analysis of all known TH transporter genes.
Methods: Following RT-PCR screening using mouse anterior pituitary cDNA, all detected transporters were quantified by qRT-PCR. Expression within the thyrotropes was confirmed by *in situ* hybridization (ISH).
Results: Eight transporters including *MCT8* were detected. The mRNA expression levels of these transporters, namely, *Mct8*, *Oatp1a1*, *Oatp1a4*, *Oatp2b1*, *Oatp3a1*, *Oatp4a1*, *Lat1*, and *Lat2* were 1.0, 2.0, 1.4, 1.7, 22.5, 3.5, 66.6, and 74.9, respectively. Oatp3a1 and Lat1 expression in the thyrotropes were confirmed by ISH.
Conclusion: Considering the higher specificity for TH, it is probable that Oatp3a1, rather than Lat1 and 2, plays a key role in the negative feedback of T_4 in TSH producing cells. Functional analysis should further clarify the physiological role of Oatp3a1 in the thyrotrope.

P1-d2-514 Pituitary and Neuroendocrinology 2

Abstract has been withdrawn

P1-d2-515 Pituitary and Neuroendocrinology 2

Anterior hypopituitarism in adult childhood cancer survivors (CCS): a report from the St. Jude Lifetime cohort

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Background: The prevalence and risk factors associated with hypopituitarism during the decades that follow cancer treatment are not well established in adult CCS.
Objectives: To estimate the prevalence of deficiencies in GH (GHD), LH/FSH (LH/FSHD), TSH (TSHD), and ACTH (ACTHD) and identify associated patient characteristics and treatment variables.
Methods: 2,240 subjects (1,147 males) were evaluated. Mean age 33.1 (range 18.3-63.8) yr, mean time since initial diagnosis 24.8 (10.2-48.3) yr. 822 were treated with cranial radiotherapy (CRT) at a mean age of 7.9 (0.1-26) yr. TSH, Free T4, LH/FSH, sex steroids were assessed in all; IGF-1 and cortisol only in those treated with CRT. Plasma IGF-1< -2 z-score was a surrogate for GHD. CRT was quantified by the maximum tumor prescribed dose. The effects of clinical variables were tested in univariate logistic regression models followed by a multiple logistic regression analysis for the identification of independent associations.
Results: The overall prevalence of LH/FSHD and TSHD was 4.8% and 3.9% respectively. Following CRT, the prevalence of GHD, LH/FSHD, TSHD and ACTHD was 47.3%, 12.0%, 9.9% and 5.4% respectively. The prevalence of GHD was 28.8% below 18Gy, 48.8% ≥ 18 Gy (p< 0.001). The prevalence of LH/FSHD, TSHD and ACTHD was 8.0%, 6.5% and 2.1% respectively below 40 Gy and 25.1%, 21.5% and 17% respectively ≥ 40 Gy (p< 0.0001). Independent associations found with CRT doses are outlined in Table 1. Females were less likely to have LH/FSHD (OR 0.5;95% CI 0.32-0.8;p=0.004) or ACTHD (OR 0.5;95%CI 0.26-0.94;p=0.03).

CRT Dose, Gy	GHD	LH/FSHD	TSHD	ACTHD
0-14.9	OR 8.1; 95% CI 4.2-15.6; p<0.0001	OR 2.8; 95% CI 0.33-23.1;p=0.35	OR 12.7; 95% CI 2.9-54.8; p<0.001	Combined with range below
15-21.9	OR 13.8; 95% CI 9.5-20.3; p<0.0001	OR 3.4;95% CI 1.2-9.8; p=0.02	OR 16.1; 95% CI 5.8-44.5; p<0.0001	OR 2.4; 95% CI 0.7-7.7;p=0.16
22-29.9	OR 27.2; 95% CI 18.5-39.9; p<0.0001	OR 10.8; 95% CI 4.9-23.8; p<0.0001	OR 15.9; 95 CI% 5.8-43.3; p<0.0001	OR 6.8; 95% CI 2.3-20.1; p<0.001
30-39.9	OR 6.3; 95% CI 2.8-14.2; p<0.0001	OR 34.4; 95% CI 11.8-100.1; p<0.0001	OR 31.1; 95% CI 7.9-122.4; p<0.0001	OR 20.8; 95% CI 4.9-88.2; p<0.0001
≥40	OR 15.4; 95% CI 10.5-22.8; p<0.0001	OR 41.7; 95% CI 19.6-88.5; p<0.0001	OR 51.3; 95% CI 20.6-127.7; p<0.0001	OR 20.1; 95% CI 9.4-43.1; p<0.0001

[Table 1]

Conclusions: GHD, LH/FSHD, TSHD and ACTHD are common following CRT. Gender differences should be further investigated.

P1-d2-516 Pituitary and Neuroendocrinology 2

Unusual presentation of craniopharyngioma with acute haemorrhage and syndrome of inappropriate antidiuretic hormone secretion (SIADH)

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Background: Craniopharyngioma presenting with haemorrhage is extremely rare. Prior to the advent of CT scans only two cases of craniopharyngiomas with intramural haemorrhage were reported, both in adults (1956 and 1977). A further 9 cases in adults have since been reported, mainly subsequent to treatment. Even rarer is the pre-operative association of SIADH with craniopharyngioma. A review of 121 patients with craniopharyngioma diagnosed between 1964-2003 reported none presenting with SIADH. Neither of these features has been present in 35 paediatric patients consecutively presenting with craniopharyngioma/rathke's cyst to our centre in over 20yrs.
Objective/hypothesis/method: Clinical case report and literature review.
Results: A 15yr old boy presented to Emergency Department with history of severe headaches over several days, tonic extension of limbs and dilatation of pupils. His consciousness fluctuated between GCS score 9 and 12. At presentation he was hyponatraemic (Na 128mmol/l) and urine osmolality was 337mOsmo/kg consistent with SIADH (this resolved spontaneously within 48hrs with no further abnormal neurological signs). CT scan was consistent with craniopharyngioma with intramural bleed, supported by MRI scan (multicystic sellar/suprasellar tumour with areas of dense calcification). Pubertal staging was G3, PH1, TV 6mls, he had full visual fields and normal baseline endocrinology. Endoscopic transphenoidal debulking of tumour was performed, achieving near complete removal. Post-operatively he had panhypopituitarism with diabetes insipidus; and recovery was complicated by transphenoidal CSF leak. Full hormone replacement has been commenced. Six months post-surgery he has proceeded to adjuvant proton beam radiotherapy for the small residual tumour.
Conclusion: To our knowledge SIADH has not been reported as a presenting feature of craniopharyngioma. We consider that this may have been secondary to effects of the recognised rare acute haemorrhage within the tumour.

P1-d2-517 Pituitary and Neuroendocrinology 2

Managing rare, resistant, macro- and giant prolactinomas causing raised intracranial pressure in children: lessons learnt at a single centre

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Introduction: Childhood macroprolactinomas are extremely rare and usually present to neurosurgery/oncology rather than endocrinology units, with little evidence base for age-appropriate management. The relative cost-benefits, dose intensity and timing of different medical and surgical therapies are thus unclear.
Case studies: We report 6 children aged 11-16 years with complex macroprolactinomas: 5 newly presenting in 2010-12 with RICP, GH/Gn deficiency and visual impairment (4); and 1 in 2009, panhypopituitary/DI 4 years post-surgery for misdiagnosed craniopharyngioma. The diagnosis was unsuspected clinically and radiologically and only made on grossly elevated prolactin levels, preoperatively in 5. 2/6 had family members with pituitary tumours. All underwent MEN-1 and AIP gene mutation screening.
Despite initial response to cabergoline 0.25-0.5mg/week, 4/6 proved resistant to maximal dosing needing debulking surgery to preserve vision. Nevertheless, 2 are blind, 3 have panhypopituitarism/DI and 3 needed radiotherapy. Paradoxically, the largest tumour with prolactin >1000,000u/ml proved cabergoline responsive and least morbid, whilst the 11 year old with prolactin 3000u/ml suffered a stroke and blindness during pre-radiation debulking surgery. He proved heterozygous for MEN-1 splicing mutation intron 4c.784-9G>A.
Conclusion: To avoid misdiagnosis and surgery-induced endocrinopathies, prolactin levels should be measured in all suprasellar tumours. Fast dose-escalating Cabergoline may avoid surgery, even in giant tumours with visual compromise. In resistant disease, surgery rarely achieves control or visual preservation and increases hypothalamo-pituitary deficits whereas radiation appears effective and less morbid. Genetic screening identifies Index cases and at-risk relatives. Age-appropriate, multidisciplinary centralised decision-making and outcome monitoring will enhance understanding of prognostic biomarkers and reduce morbidity in this rare neuroendocrine tumour.

P1-d2-518 Pituitary and Neuroendocrinology 2

A single sample triptorelin stimulation test in diagnosing the onset of hypothalamic-pituitary-gonadal axis in girls

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Background: Gonadotropin-releasing hormone (GnRH) stimulation test is a gold standard for confirming the diagnosing the onset of hypothalamic-pituitary-gonadal axis (HPGA) in children, an accurate but at times not always comfortable method.
Objective and hypotheses: To determine the clinical value of a single sample triptorelin (decapeptyl, a GnRH analogue) stimulation test in diagnosing the onset of HPGA for girls.
Methods: One hundred and eight triptorelin stimulation tests were performed in 108 girls. Following administration of triptorelin, blood samples for luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were obtained at 0, 20th, 40th and 60th minutes in 90/108 girls. Among the other 18/108 girls, blood samples were obtained at 0, 30th and 60th minutes in 16/18, at 0 and 60th minutes in 1/18, and at 0 and 40th minutes in 1/18. Gonadotropin in serum were assayed by immunochemiluminometric assays (ICMA).
Results: There were 79 girls of the onset and 29 of the non-onset for HPGA. In 90/108 girls, serum peak LH (PLH) for the onset of HPGA and the non-onset of HPGA were respectively (20.24±15.39) and (2.56±1.03) IU/L ($P \leq 0.01$). The area under the receiver operating characteristic curve of 40min LH (91/108) for diagnosing the onset of HPGA was 0.990, and for 60min LH (107/108) 0.982, and for PLH (90/108) 0.990. When 40min LH, 60min LH and PLH were respectively no less than 4.09 IU/L, 4.04 IU/L and 4.22 IU/L, the sensitivities for diagnosis the onset of HPGA were 93.9%, 96.2% and 96.9%, respectively, and all specificities were 100.0%. When 40min and 60min LH were respectively no less than 4.22 IU/L, the sensitivities for diagnosing the onset of HPGA were 90.9% and 96.2%, and all specificities were 100.0%.
Conclusions: A single serum gonadotropin sample collected 40 minutes or 60 minutes during triptorelin stimulation test is adequate for diagnosing the onset of HPGA for girls and as reliable as triptorelin stimulation test (one-hour method,ICMA).

P1-d2-519 Pituitary and Neuroendocrinology 2

Management of central diabetes insipidus with oral desmopressin lyophilisate in infants

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Background: Experience with oral lyophilized desmopressin for diabetes insipidus in neonates and infants is limited.
Objective and hypotheses: We aimed to assess the efficiency of oral lyophilized desmopressin in neonatal diabetes insipidus.
Methods: Clinical, laboratory, and imaging characteristics of four newborns with central diabetes insipidus treated with oral lyophilized desmopressin were evaluated.
Results: Two boys and two girls with a mean age of 19±17 days were evaluated. The newborns (mean gestational age, 38.5±1.9 weeks; mean birth weight, 3355±244 g; mean weight at admission, 3169±225 g) presented with

polyuria and hypernatremia (mean, 168±9 mmol/L). At the time of hypernatremia, mean serum and urine osmolality values were 310±16 mOsm/kg and 179±48 mOsm/kg, respectively. ADH levels were < 0.5 pmol/L in all cases. Magnetic resonance imaging revealed schizencephaly and ectopic posterior pituitary gland (n=1), schizencephaly and corpus callosum agenesis, septo-optic dysplasia and pituitary hypoplasia (n=1), and the absence of the septum pellucidum (n=1). Oral lyophilized desmopressin (60 µg/tablet) dissolved in water (3-5 ml) was initiated with a dose of 3 µg/kg/day in two equal doses together with limitation of water intake to avoid hyponatremia. Serum sodium levels returned to normal in a mean duration of 58±9.9 hours with a mean decline rate of 0.37±0.1 mmol/L/hour following desmopressin administration. Rehospitalization was required two times for one of the infants because of hypernatremia due to non-compliance. No episode of hyponatremia was encountered. Weight gain and growth of the infants were normal during the mean follow-up duration of 8.5±1 months.
Conclusions: Oral lyophilized desmopressin appears to be practical and safe in the treatment of central diabetes insipidus during the first year of life.

P1-d2-520 Pituitary and Neuroendocrinology 2

Pulsatility of the hypothalamus-pituitary-adrenal (HPA) axis in depressed male survivors of childhood traumatic brain injury (TBI)

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Background: TBI is the most frequent cause of acquired brain injury in childhood. Although GH deficiency is the most common anterior pituitary complication following TBI not much is known about the impact of TBI on long term HPA axis function and associations with neuropsychiatric disorder.
Objective and hypotheses: To investigate the HPA axis in a potentially high-risk group: children following moderate/severe TBI.
Methods: 15 male participants with a history of moderate or severe TBI based on admission Glasgow Coma Scale (GCS moderate 9-12, severe 3-8). Mean age at injury was 11.1 (range 6-16), time from injury was 8.7 (range 7-10), mean age at assessment was 20 (range 15-26) years and all participants were in late or post puberty (Tanner stage 4/5). Following clinical assessment (including screening for depression with the BDI-II and DSM oriented scales on ASR and ABCL profiles), they underwent an overnight 12 hour cortisol venous profile (15 min sampling) followed by an ITT the following morning. PulseXP deconvolution software was used to analyse cortisol pulsatile pattern and secretion rate.
Results: All participants were euthyroid and showed a normal cortisol response to the ITT. Four participants had depression scores within the clinical range. Deconvolution analysis of overnight profiles showed higher frequency of cortisol pulses in the depressed participants (8.7±1.5 vs 6.1±1.6, p=0.015). There were no significant differences in average or total cortisol secretion, maximal cortisol concentration, or amplitude-related measurements (mean secretion pulse mass and height). Approximate entropy - a measure of orderly hormone secretion - was also not different between groups.
Conclusions: Increased HPA axis activity is seen in survivors of TBI in childhood. The heightened activity is due to an increase in the number of pulsatile activity, a pattern described in depressed patients without a history of TBI.

P1-d2-521 Pituitary and Neuroendocrinology 2

Trans-sphenoidal approach for the treatment of childhood craniopharyngiomas can reduce the risk of hypothalamic obesity

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Background: Obesity is common and difficult complication after childhood craniopharyngioma surgery which has been reported to occur up to 75% of survivors. Hypothalamic damage during surgery is one of the most important risk factors to predict obesity.
Objective and hypotheses: Recently most craniopharyngiomas are removed by transsphenoidal approach (TSA) which is less invasive to the surrounding neural and vascular structures compared to transcranial approach (TCA). In this study 20 children undergoing various combinations of TSA and TCA were retrospectively investigated to confirm whether postoperative obesity is less common in TSA than TCA.
Subjects and methods: Twenty children with craniopharyngioma (9 boys and 11girls, ranging from 3.2yr to 15.8yr) underwent gross total tumor removal. Thirteen of them were operated by TSA, two were by TCA and five were by TCA followed by TSA. The height and weight of these patients were analyzed for more than two years after their last surgery. BMI-SDS and BMI percentile for age and gender were calculated based on the local standards.
Results: The changes of Mean (SD) values of BMI-SDS by years after the last surgery are shown below.

	At last surgery	6m	1y	2y	3y	4y
All patients	0.53 (1.30)	1.02 (1.35)	0.89 (1.39)	0.62 (1.43)	0.64 (1.51)	0.46 (1.61)
Single TSA	0.18 (1.16)	0.53 (1.36)	0.44 (1.47)	0.17 (1.52)	0.21 (1.77)	-0.20 (1.85)
Multiple surgeries	1.80 (0.76)	2.18 (0.77)	1.93 (0.69)	1.68 (0.60)	1.45 (0.66)	1.47 (0.80)

[Table1]

The mean values of BMI-SDS were higher in the patients with multiple surgeries than in the patients with single TSA. Transient increase in BMI-SDS returned to baseline after 2 years. Incidence of obesity (BMI>95th percentile) at last TSA was 15% in the patients with single TSA and 80% in the patients with multiple surgeries. The dose of hydrocortisone did not affect the severity of obesity.
Conclusions: It has been concluded that TSA for craniopharyngiomas is less invasive and both incidence and severity of postoperative obesity are lower than TCA even after gross total tumor resection.

P1-d1-522 Programming/Epigenetics 1

Altered protein arginine methylation in offspring of diabetic mice

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Background: Offspring of diabetic mothers display an increased risk for metabolic abnormalities including the development of diabetes later in life. Asymmetric dimethylarginine (ADMA) is an early marker in the development of diabetes (Lee JH, 2011) and a potent inhibitor of nitric oxide synthases (NOS). Protein arginine-N methyl transferases (PRMTs) are key enzymes in the formation of ADMA.
Objective and hypotheses: To investigate the effects of maternal hyperglycemia on offspring ADMA and nitric oxide metabolite (NOx) formation, we utilized an autosomal dominant mouse model of diabetes. (C57Bl6/J-Ins2 < Akita>)
Methods: Serum levels of NOx, ADMA, SDMA (symmetric dimethylarginine), L-arginine, citrulline and ornithine as well as polyamines were assessed in 6, 14 and 26 week old male wildtype offspring. Hypothalamic gene expression arrays were obtained in 14 week old male mice.
Results: NOx is significantly decreased in 6 week old mice and correlates with impaired glucose tolerance in older offspring of maternal diabetes. Serum levels of ADMA but not SDMA, are increased in offspring of maternal diabetes. L-Arginine, citrulline and ornithine, and polyamine serum levels do not differ to control offspring. Gene expression of PRMT1, 8 and 10 is upregulated ($p< 0.02$), expression of NOS1 is downregulated ($p< 0.02$) in hypothalamic samples of 14 week old WT offspring from diabetic mothers.
Conclusions: Nitric oxide metabolism and protein arginine methylation are altered in offspring exposed to maternal hyperglycemia. Changes in ADMA and NOx precede metabolic changes. Altered arginine methylation and the development of metabolic changes in these mice might arise from gene expression changes of PRMTs and NOS, possibly through epigenetic modifications.

P1-d1-523 Programming/Epigenetics 1

Molecular and clinical studies in 138 Japanese patients with Silver-Russell syndrome

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Background: Silver-Russell syndrome (SRS) is a congenital developmental disorder characterized by pre- and postnatal growth retardation and a constellation of somatic features. Recent studies have revealed relative frequency and characteristic phenotype of two major causative factors for SRS, i.e. epimutation of the *H19*-DMR and uniparental maternal disomy 7 (upd(7)mat), as well as multilocus methylation abnormalities and rare genomic alterations.
Objective: To report molecular and clinical findings in 138 Japanese SRS patients.
Methods: We performed methylation analyses of the *H19*-DMR and the *MEST*-DMR in 138 SRS patients, and multiple DMR analyses in 38 SRS patients. We also performed oligoarray CGH in all patients, using a genome-wide 4x180K Agilent platform catalog array and a custom-build high density oligoarray for some regions.
Results: We identified *H19*-DMR epimutation and upd(7)mat in 31.2% and 6.5% of 138 Japanese SRS patients, respectively. Epimutations were associated with more reduced birth length and weight, more preserved birth occipitofrontal circumference, more frequent somatic features. The degree of placental hypoplasia was similar between the two groups. In patients with epimutation, methylation indices for the *H19*-DMR were positively correlated with the birth length and weight, the present height and weight, and the placental weight. Multilocus analysis revealed co-existing hyper- and hypomethylated DMRs predominantly in epimutations, with frequencies of 35.7% of examined patients and 2.4% of examined DMRs. Oligoarray CGH identified a ~3.86 Mb deletion at chromosome 17q24 in an idiopathic case.
Conclusions: The results are grossly consistent with the previously reported data, although the frequency of epimutations is lower in the Japanese SRS patients than in the Western European SRS patients. Furthermore, the results provide useful information regarding placental hypoplasia in SRS, and underlying causative factors for idiopathic SRS.

P1-d1-524 Programming/Epigenetics 1

Reduced insulin sensitivity in children born to mothers with severe hyperemesis gravidarum

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Background: Hyperemesis gravidarum (HG) leads to restriction in maternal and fetal nutrition during pregnancy. There are no data on the long-term metabolic health outcomes in the offspring.
Hypothesis: HG leads to fetal nutritional compromise or physiological stress, programming later metabolism and body composition.
Methods: Two groups of healthy pre-pubertal children born at term, aged 4-11 years were studied: offspring of mothers who suffered HG (n=36) and offspring of mother who did not (control group, n=54). Recruited HG children were born to mothers admitted to hospital at < 20 wks gestation with hyperemesis that began early and usually persisted throughout pregancy. Following an overnight fast, a frequently sampled intravenous glucose tolerance test modified by insulin was performed, and insulin sensitivity was measured using Bergman's minimal model. Other assessments included fasting lipid and hormonal profiles, as well as body composition (DEXA). Data were analysed separately using linear mixed models and expressed as mean±SEM.
Results: Subjects studied were 8.7±1.9 yrs with no difference in age, sex, gestational age nor birth weight between groups. Subjects born to mothers with severe HG (N=36) had a 33% reduction in insulin sensitivity (10.4±0.6 vs 13.4±0.9 $x10^{-4}min^{-1}\cdot(mU/L)$; p=0.016), increased fasting insulin (6.5±0.6 vs 4.9±0.3 mIU/L; p=0.023), reduced IGFBP1 (13.0±1.3 vs 18.0±1.6 ng/ml; p=0.029) and IGFBP3 (3017±106 vs 3497±102 ng/ml; p=0.008) in comparison to controls. 8 am cortisol was higher in HG children (251±13 vs 218±11 nmol/l; p=0.007). DEXA-derived body composition was similar in HG and control groups (%body fat 19.2 vs 18.2 p=0.49).
Conclusion: Children born to mothers who experienced severe HG were less insulin sensitive and had elevated baseline cortisol compared to controls. We postulate that severe HG reduces insulin sensitivity in the offspring due to fetal programming of the fetal HPA axis.

P1-d1-525 Programming/Epigenetics 1

Early markers of the metabolic syndrome in children born post-term

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Background: There are no data on the metabolic consequences of post-term birth (≥42 weeks gestation). Post term birth is associated with prolonged gestation and possible late fetal nutritional compromise. We have recently reported increased adiposity in late adolescent post-term boys.
Hypothesis: Post-term birth leads to programmed adverse glucose metabolism and body composition in childhood.
Methods: 90 healthy pre-pubertal children (4-11 years), born appropriate for gestational age were studied; 36 born post-term (18 boys) and 54 (36 boys) born at term (restricted to 38-40 weeks). Primary outcome was insulin sensitivity measured using freq sampled intravenous glucose tolerance tests and Bergman's minimal model. Other assessments included lipid and hormonal profiles, body composition, 24-hour ambulatory blood pressure monitoring, and inflammatory markers.
Results: Insulin sensitivity was 36% lower in post-term than in term children (7.31 vs. 11.39 $10^{-4}\cdot min^{-1}\cdot(mU/l)$; p< 0.0001). Lower insulin sensitivity was observed in both post-term boys and girls, but a compensatory increase in acute insulin response occurred only among boys (+59%; p=0.007). Post-term children had higher LDL-C concentrations (+20%; p=0.019), greater total cholesterol to HDL-C ratio (+14%; p=0.015), and tend to have higher triglyceride levels (+20%; p=0.055). Post-term children displayed other markers of the metabolic syndrome: greater abdominal adiposity (+15%; p=0.007), reduced normal nocturnal systolic (-30%; p=0.004) and diastolic (-23%; p=0.045) blood pressure dipping, lower adiponectin concentrations (-21%; p=0.020), as well as higher leptin (+41%; p=0.010) and uric acid (+13%; p=0.044) concentrations.
Conclusions: Post-term children have lower insulin sensitivity and display early markers of the metabolic syndrome. These findings could have major implications for the management of prolonged pregnancies.

P1-d1-526 Programming/Epigenetics 1

Methylation of the PGC-1alpha promoter is associated with the mitochondrial content and insulin resistance in liver of IUGR rats with catch-up growth

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Background: Epigenetic modification via DNA methylation is associated with metabolic disease. Intrauterine growth retardation (IUGR) individuals with catch-up growth are prone to insulin resistance.
Objective and hypotheses: We hypothesized that methylation of the peroxisome proliferator-activated receptor gamma (PPARgamma) coactivator-1 alpha (PGC-1alpha) promoter is associated with insulin resistance in liver of catch-up growth IUGR rats (CG-IUGR).
Methods: An IUGR rat model was established through maternal nutritional restriction. After the PCR amplification of the bisulfite treated DNA from liver tissue, Pyrosequencing was used to analyse the methylation of the PGC-1alpha promoter. The mitochondrial content and the mRNA level of PGC-1alpha were assessed by real-time PCR.
Results: CG-IUGR showed increase in methylation level of specific sites -787 and -803 in PGC-1alpha promoter, and decrease in PGC-1alpha expression and mitochondrial content compare with control. The methylation level of specific sites in PGC-1alpha promoter was inversely correlated with the abundance of PGC-1alpha mRNA and the mitochondrial content, however, positively correlated with plasma fasting insulin level and the triglyceride level in liver tissue.
Conclusions: Our findings suggest that methylation of the PGC-1alpha promoter probably plays a potential role in metabolic programming in CG-IUGR rats.

P1-d1-527 Programming/Epigenetics 1

Methylation defects of *GNAS* cluster in two patients with PHP-Ia

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Background: Pseudohypoparathyroidism (PTH) is rare heterogeneous disorder characterized by resistance to PTH due to deficiency of Gsα, encoded by the *GNAS* gene. This condition is divided into two types. PHP-Ia is associated with Albright's hereditary osteodystrophy (AHO) and is usually caused by mutations in Gsα-coding *GNAS* exons, whereas PHP-Ib lacks AHO-phenotype and usually results from methylation defects in *GNAS* cluster. However, recent studies have identified methylation defects in a few patients with PHP-Ia.
Objective and hypotheses: To report methylation defects in patients with PHP-Ia.
Methods: We studied two sporadic cases with PHP-Ia, one with mild AHO features and the other with severe AHO features. Gsα-coding *GNAS* exons were analyzed by direct sequencing, and methylation status of the four *GNAS* differentially methylated regions (DMRs) were quantified by MS-MLPA and pyrosequencing.
Results: No mutation was found in Gsα-coding *GNAS* exons, However, *AS*-DMR, *XL*-DMR, and *A/B*-DMR were hypomethylated, and *NESP55*-DMR was hypermethylated in both patients.
Conclusions: These results suggest that PHP-Ia can be caused by methylation abnormality of the GNAS DMRs, as well as mutations of Gsα-coding exons. Thus, methylation defects should be considered in PHP-Ia patients who have no demonstrable mutations of Gsα-coding *GNAS* exons.

P1-d1-528 Programming/Epigenetics 1

Intrafamilial correlations of metabolic risk factors: results from the Ulm Birth Cohort Study (UBCS)

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Background: The metabolic syndrome (MetS) comprises glucose intolerance, central obesity, hypertension and dyslipidaemia. The role of additional metabolic factors like Apolipoprotein B (ApoB) and Retinol-Binding-Protein 4 (RBP4) is discussed in literature. There is familial aggregation of the factors of MetS, however parent dependent intrafamiliar associations of metabolic risk factors are poorly understood.
Hypothesis: Correlation of insulin-regulated parameters like ApoB and RBP4 is stronger between mothers and offsprings than between fathers and offsprings.
Methods: During the 8-year follow-up of the Ulm Birth Cohort Study (UBCS), 8 yrs old children and their parents underwent anthropometric measurements and fasting plasma sampling. Levels of insulin, glucose, ApoB, RBP4, leptin, and adiponectin were measured. Data of n=303 trios (child, mother, father) were examined for intrafamilial associations of metabolic risk factors (crude and partially adjusted correlation analyses; confounders: gender, BMI.
Results: Correlation of fasting plasma levels of insulin, ApoB and RBP4 was stronger between mothers and children than between fathers and children. Correlations between maternal and offsprings fasting plasma insulin levels became stronger after partial adjustment for confounders (rcrude=0.23 vs. radj=0.29). The correlations between maternal and offsprings ApoB levels were not affected by partial adjustment for confounders (rcrude=0.37 vs. radj=0.36). Correlation of RBP4 remained stronger between mothers and children than between fathers and children after partial adjustment for confounders (radj=0.27 vs. radj=0.17). Correlation of leptin and adiponectin levels was comparable between children and their fathers or their mothers.
Conclusion: Correlation of fasting insulin, ApoB and RBP4 was stronger between mothers and children than between fathers and children. Perinatal programming of children's metabolic system by maternal factors is suspected.

P1-d1-529 Puberty and Gonads 1

Treatment of 11 newborns with congenital hypogonadotropic hypogonadism with continuous subcutaneous infusion of recombinant FSH and LH

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Background: Congenital hypogonadotropic hypogonadism (CHH), isolated or associated with other pituitary hormones deficiencies, leads to absence of the physiological postnatal gonadotropin peak (called "mini puberty"). Standard treatments, usually started after the age of puberty, often only partially correct the genital abnormalities and spermatogenesis.
Objective and hypotheses: Treat male infants with CHH with subcutaneous infusion of recombinant FSH and LH for compensate the lacking of neonatal peak of gonadotropins, and next assessed the proliferation of Leydig and Sertoli cells.
Methods: 11 infants with a CHH (7 with a congenital hypopituitarism and 4 with a Kallman syndrom) younger less than 12 months, received 6 months of recombinant subcutaneous human FSH and LH via an insulin pump. Clinical (testicular size, penis length), sonographic (testicular lenght) and biological parameters (FSH, inhibin B, AMH, LH, and testosterone) were recorded.
Results: Treatment increased circulating LH levels from 0.2 ± 0.2 to 5.4 ± 6 IU/l and testosterone from 0.03 ± 0.03 ng/ml to 1.9 ± 0.9 ng/ml. Mean penis length increased from 16 ± 5,1 to 38 ± 9,2 mm. Treatment increased FSH

levels from 0.3 ± 0.3 to 24.5 ± 13 IU/l, inhibine B levels from 79 ± 62 to 333 ±65 pg/ml and AMH from 679 ± 558 to 815 ± 312 pmol/l. Testicular lenght increased from 10 ± 1,2 to 19 ± 3,7 mm during treatment.
Conclusions: Infusion of recombinant LH stimulates Leydig cells differentiation and the production of testosterone. Infusion of recombinant FSH stimulates the Sertoli cells proliferation and production of inhibine B and AMH. Despite high levels of LH and testosterone, we did not observe decreased production of AMH or inhibine B, as normally observed during puberty. We can therefore hypothesize that androgens have no inhibitory effect on Sertoli cells during the first year of life.

P1-d1-530 Puberty and Gonads 1

Effects of metformin and oral contraceptive on serum anti-Mullerian hormone levels in adolescent patients with polycystic ovary syndrome

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Background: Anti-Mullerian hormone (AMH) has been found to be increased in the serum of women and adolescent with polycystic ovary syndrome (PCOS). AMH levels are not influenced by hormonal fluctuations and remain constant throughout the menstrual cycle, making it a promising diagnostic marker for patients with PCOS.
Objective and hypotheses: To assess the impact of oral contraceptive (OC) containing drospirenon and metformin+OC, on serum AMH levels, in a cohort of adolescents with PCOS.
Methods: Forty- nine adolescents (aged 13- 17.5 years) with PCOS diagnosed according to the criteria proposed in 2003 by the Rotterdam PCOS consensus workshop group. Patients were divided into two groups according to the result of OGTT. Group 1 consisted of patients without insulin resistance; group 2 consisted of patients with insulin resistance. Group 1 received an OC containing 0.03 mg ethinylestradiol+3 mg drospirenone and group 2 received OC+metformin. The effect of OC and OC plus metformin therapy on the serum AMH, E2, LH, FSH, fasting glucose and insulin, total testosteron, 1,4 androstenedion, DHEA-S, SHBG levels was studied. Serum was collected from the subjects during the early follicular phase of the menstrual cycle and after the sixth month of therapy. In addition, ovarian volume was assessed.
Results: Serum AMH levels and ovarian volume were decreased significantly both of the groups (table). There was no difference between the two groups in the term of AMH falling (p=0.315, t= 1.017).
Conclusions: AMH could be used as a tool to evaluate treatment efficacy of PCOS.

	Group 1	Group 1	Group 1	Group 2	Group 2	Group 2
	Before treatment	After treatment	p	Before treatment	After treatment	p
Age (years)	15.6 ± 1.3			15.2 ± 1.4		
AMH (ng/ml)	6.7±3.7	4.3±3.1	0.006	4.7±3.07	3.1±2.05	0.048
SHBG (nmol/L)	38±14.8	180(158)	0.004	27.9±10.7	190(131)	0.002
ROV (ml)	11.3±3.4	5.3(5.2)	<0.001	8.6±3.3	5.9(4)	0.085
LOV (ml)	9.3±4	4.9(3.7)	<0.001	8.4±3.1	6.2(3.8)	0.048

[Outcome of the patients]

P1-d1-531 Puberty and Gonads 1

Excess of ovarian nerve growth factor (NGF) causes a polycystic ovary-like syndrome (PCOS) in mice, which closely resembles both reproductive and metabolic aspects of the human syndrome

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Background: PCOS, the most common female endocrine disorder of unknown etiology is characterized by reproductive abnormalities and associated metabolic conditions comprising insulin resistance, Type 2 diabetes mellitus and dyslipidemia.
We previously reported that transgenic overexpression of NGF, a marker of sympathetic hyperactivity, directed to the ovary by the mouse 17α-hydroxylase promoter (17NF mice), results in ovarian abnormalities similar to that seen in PCOS women (Dissen et al, 2009).
Objective and hypotheses: In the present study we sought to investigate the metabolic profile exhibited by these transgenic mice.
Methods: We studied 17NF mice and its wild type littermate at 10, 15 and 20 weeks of age. We determined glucose homeostasis by glucose tolerance test (GTT) and body composition and bone mineral density (BMD) by Dexa scan. We also measured interscapular brown adipose tissue temperature (iBAT-T) and UCP1 expression as a marker of sympathetic nerve activity
Results: We found that at 10 weeks of age 17NF mice display glucose intolerance ($p< 0.01$). This occurred despite no difference in body weight or total body fat, although 17NF mice showed an increase in visceral fat ($p< 0.05$). This impairment in glucose tolerance was maintained to 15 and 20 weeks of age when 17NF mice also displayed significantly increased body weight, body fat and visceral fat compared with WT mice. Interestingly, 17NF mice also exhibited an increased BMD from 15 weeks of age compared with WT ($p< 0.05$).
Twenty four hours iBAT-T was higher in 17NF mice than WT at 10 and 20 weeks of age and was significantly different when just the dark period was considered ($p< 0.05$) .
Conclusions: These findings suggest an overexpression of NGF in the ovary may be sufficient to cause both reproductive and metabolic alterations that are characteristic of PCOS. Most importantly, this new animal model could therefore allow for the exploration of new treatments of PCOS.

P1-d1-532 Puberty and Gonads 1

Replacement therapy with recombinant human FSH in Japanese males with congenital hypogonadotropic hypogonadism

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Background: FSH stimulates Sertoli-cell proliferation and number during testis development. In men with gonadotropin deficiency, FSH has usually been replaced with or after human chorionic gonadotropin (hCG) administration. But some men with severe gonadotropin deficiency, e.g. congenital hypogonadotropic hypogonadism (HH), often had small testis volume and a low sperm count. In prepubertal period, endogenous FSH secretion in men with congenital HH is undetectable or very low compared with acquired HH. We hypothesized that replacement therapy with recombinant human FSH (r-hFSH) prior to hCG in men with congenital HH improves spermatogenesis.
Objective: To evaluate the effects of r-hFSH on testicular growth in Japanese males with congenital HH.
Methods: We studied four males (aged 15.8-24.8 years) with congenital HH (Kallman syndrome, normosmic idiopathic HH, MRI invisible stalk syndrome). They were treated with r-hFSH (75 IU daily s.c.) for 6 months. Main outcome mesures were changes in serum levels of FSH, LH, testosterone, anti-Müllerian hormone (AMH), and testicular volume.

Results: Serum FSH concentration elevated from 0.36-1.00 IU/L to 4.14-5.54 IU/L, and reached the range observed in early stage of puberty. There was no increase in serum LH and testosterone concentrations. Serum AMH concentration increased up to prepubertal range, from 150-246 pmol/L to 246-653 pmol/L. Testicular volume was increased twofold, from 1.4 ± 0.5 mL to 2.8 ± 0.7 mL ($p < 0.001$).
Conclusions: r-hFSH alone induces growth of testes and increase of serum AMH concentration. These findings suggest that r-hFSH stimulates Sertoli-cell proliferation before induction of puberty with hCG, which may contribute to spermatogenesis later in life.

P1-d1-533 Puberty and Gonads 1

Evaluation of puberty and gonadal function in women with congenital disorders of glycosylation (CDG) syndrome

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Background: The Congenital Disorders of Glycosylation (CDG) syndromes are a group of rare autosomal recessive disorders affecting glycoprotein synthesis. Type CDG I is the most frequent form and is characterised by multisystem manifestations, in particular the nervous system. Premature ovarian failure (POF) has been usual described in CDG women. POF is often overlooked in adolescents and consist a long term complication.
Objective: We sought to describe gonadal function in CDG patients and thrombosis and bleeding risk.
Materiel and methods: We reported the clinical criteria, biological and ultrasonographic characteristics of eighteen women with CDG syndrome (16 with CDG Ia and 2 with CDG 1b aged from 8,6 to 35 years old (16.5±7.5) followed in Necker Hospital.
Results: In the 10 patients with CDG1a aged of more 13 years old, none had spontaneous puberty. FSH levels (n=11) were very high 88 mUI/ml, Estradiol was low than 10 pg/ml and AMH was undectable at POF diagnosis (13.9±2.8 years). In 91.6% patients, ovaries were unseen or appeared very in pelvic ultrasound (n=12). Only in one patient, 3 follicles were showed. In contrast, in 2 patients with CDG 1b, one had spontaneous puberty and FSH and AMH levels were normal. Finally, 70% (n=12) had a risk of thrombosis (antithombine III, and/or protein S and/or protein C defect) and 27.3 % (n=13) had bleeding disorders.
Conclusion: POF seems severe precocious and organic in patients with CDG1a. Hormonal treatment with estrogen must be prescribed without delay, with particularly take care of thrombosis risk.

P1-d1-534 Puberty and Gonads 1

Impact of gonadotrophin analogues therapy on body mass index of children with central precocious puberty

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Background: Whilst Gonadotrophin Releasing Hormone analogues (GnRHa) are widely used in the management of Central Precocious Puberty (CPP), there is little literature on their impact on Body Mass Index (BMI).
Objective and hypotheses: To determine the impact of long-acting GnRHa therapy on the BMI of children with CPP.
Methods: A retrospective analysis of case records was performed of children treated with long acting GnRHa (for a minimum of one year) for CPP between January1991 to July 2012. Children with CAH, CPP secondary to malignancies and on concomitant Growth Hormone therapy were excluded.
Results: Of the 285 children treated with GnRHa during the study period, 47 (89.6% females, median age 7.5y) satisfied the study criteria. Indications for GnRHa therapy were: idiopathic (63% of total), underlying neurological causes (22%), thelarche variant with advanced bone age (11%), and psychological reasons (4%). BMI for age Z-score increased from a mean±SD of 1.38±1.12 at the start of therapy to1.61±1.21 at either the end of therapy with GnRHa or at the last clinic visit (p-value < 0.05), and increased steadily with duration of GnRHa therapy. BMI for age Z-score at 24 months was statistically different from 18 months and baseline ($p < 0.05$). The percentage of children who had BMI > 95th centile at 18 months, 24 month and 30 months was 45%, 56.2% and 66.7%, all of which were significantly higher than baseline: 31.9% ($p< 0.05$).

Time (in months)	BMI for age Z-score	Percentage of children with BMI ≥ 95th centile
0	1.38±1.12	31.9
6	1.36±0.27	39.3
12	1.66±0.22	37.9
18	1.64±0.25	45.5
24	2.06±0.37	56.2
30	2.03±0.40	66.7

[Table:1]

Conclusions: GnRHa therapy led to an increase in BMI in our cohort of children with CPP. Whether this increase in BMI is sustained when final height is reached needs further follow-up.

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Oral contraception versus insulin sensitisation for 18 months in non-obese adolescents with androgen excess: post-treatment differences in C-reactive protein, intima-media thickness, visceral adiposity, insulin sensitivity and menstrual regularity

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Background: An oral estro-progestagen is the standard medication given to adolescent girls with androgen excess, even when those girls are not at risk of pregnancy.
Aim: To compare on- and post-treatment effects of intervention with an oral contraceptive versus an insulin-sensitizing treatment for androgen excess in non-obese adolescents.
Design: Randomized, open-label trial.
Study population: Non-obese adolescent girls with hyperinsulinemic androgen excess and without risk of pregnancy (mean age 16 yr, BMI 23 kg/m^2, N=34).
Interventions: Ethinylestradiol-cyproteroneacetate (EE-CA) versus a low-dose combination of pioglitazone (7.5 mg/d), flutamide (62.5 mg/d) and metformin (850 mg/d) (PioFluMet) for 18 mo; post-treatment follow-up for 6 mo.
Main outcome measures: Androgen excess (hirsutism and acne scores; serum testosterone); glucose-stimulated insulinemia; circulating C-Reactive Protein (CRP); carotid intima media thickness (cIMT); body composition (absorptiometry); abdominal fat partitioning (magnetic resonance imaging); menstrual regularity.
Results: EE-CA and PioFluMet attenuated androgen excess similarly but had divergent - and even opposing - effects on other outcomes. Six months post-treatment, the PioFluMet girls had a lower glucose-induced insulinemia, a lower CRP level and a thinner intima media than the EE-CA girls, and they were viscerally less adipose, had a higher lean mass and were more likely to have regular cycles.
Conclusion: The on- and post-treatment effects of PioFluMet compared favorably to those of oral contraception in non-obese adolescents with androgen excess. The intervention whereby androgen excess is reduced in adolescence influences the post-treatment phenotype. PioFluMet-like interventions in adolescence may thus hold the potential to prevent part of the androgen-excess phenotype in adulthood, including adiposity and subfertility.

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Human testicular peritubular cells: a source of Leydig cells?

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Background: The origin of the adult Leydig cell (ALC) lineage, the main producer of testosterone, is still not fully understood. LC progenitors are thought to be located in the peritubular compartment of the seminiferous tubules. In neonatal rats these progenitor cells possess steroidogenic competence. Identification of such putative Leydig stem cells in the human testis would be of potential interest for the purpose of tissue repair.
Objective: The aim of this study was to investigate whether human testicular peritubular cells (HTPCs) are steroidogenically competent precursors of the ALC lineage.
Methods: HTPCs were isolated by outgrowth cultures from biopsies of human testes from adult men with obstructive azoospermia. After confirming expression of StAR and PDGFRα in HPTCs *in situ*, the expression of markers for pluripotency, steroidogenesis and Leydig cells was analyzed by PCR. The concentration of steroids in the culture medium was measured by RIA. Cultured HPTCs were treated with forskolin to examine the participation of the cAMP-dependent pathway in directing HPTCs towards Leydig cells.
Results: HTPCs expressed pluripotency and steroidogenesis markers, but not classical Leydig cell markers. Forskolin enhanced the expression of steroidogenic enzymes and StAR. Progesterone but not testosterone was detected in the culture medium.
Conclusions: HPTCs show detectable but low capacity to produce progesterone, but lacked expression of LH receptor. Steroid production appeared to be StAR-dependent, which increased by activation of cAMP-dependent pathway *in vitro*. Leydig cell progenitors may be among the cultured HPTCs, as suggested by expression of stem cell markers. The mechanisms of their possible differentiation into ALCs remain to be explored.
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Regulation and roles of anti-Müllerian hormone in the maturating rat testis

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Background: Anti-Müllerian hormone (AMH) secreted by Sertoli cells, works by interacting with the AMH type II receptor (AMHR2), and induces regression of the Müllerian ducts in the male embryo. AMH production by the Sertoli cells remains high throughout childhood in males. However, the physiological roles of AMH during childhood are unknown. The aim of the study is to clarify the regulation and biological effects of AMH in the maturating rat testis.
Methods and results: The developmental changes of *AMH* and *AMHR2* expressions in rat testis from 1 to 7 weeks of age were investigated by quantitative real-time RT-PCR. These expressions were high from 1 to 3 weeks of age, and decreased at 7 weeks of age. Immunostaining with anti-AMHR2 antibody demonstrated that AMHR2 was expressed in early pachytene spermatocytes, but not late pachytene spermatocytes. Next, we evaluated the effect of gonadotropin on testicular *AMH* expression using hypophysectomized (HPX) rats. The pituitary was removed from 3-week-old rats, gonadotropin was injected at 5 weeks, and testicular *AMH* expression was determined at 7 weeks. The treatment of hCG did not change the expression of *AMH* in testis, although the serum testosterone level was elevated in HPX rats. In order to inhibit endogenous AMH activity, anti-AMH and anti-AMHR2 antibodies were injected into male rats from 1 to 3 weeks of age. In the rats with this treatment, the histological examination of the testis showed that development of the seminiferous tubules was accelerated when compared with that in the control.
Conclusions: These results indicate that AMH may suppress spermatogenesis and its expression is not decreased by testosterone directly.

P1-d1-538 Puberty and Gonads 1

Turner-Down syndrome mosaicism with spontaneous pregnancy and birth of a normal female

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Background: Double aneuploidy Down-Turner syndrome (DS-TS) is a rare chromosomal disorder. Most of reported cases have the typical phenotye DS with mosaicism of different varieties, only some show characteristics of both syndromes, and none present features of TS alone.
Fertility in TS is a very rare event. Nearly 5-10% of girls have spontaneous puberty and menses. In 2-7% of all cases the pregnancy is a result of a spontaneous ovulation and is associated with a high proportion of miscarriages, stillbirths, and chromosomal abnormalities.
Due to the severe complications, the pregnancy in these patients is considered of high risk.
Objective and hypotheses: To provide data of a woman with Down-Turner syndrome and pregnancy. On the follow-up she presented clinical features of Turner syndrome without clear stigmata of Down syndrome.
Methods: One patient, was referred for short stature at age 5 (Height 94.5cm< 3.22 SD WHO; Weight 12.5Kg< 2.77 SD WHO). Infancy showed delay in growth development.
Examination: high palate, clinodactyly left hand, cubitus valgus, hiperconvexas nails in hands and feet, short 4th and 5th metacarpals, dysmorphic ears, nevi, shield chest, low posterior hairline, hiperthelorism breast, epicanthus, tonsillar hypertrophy, hearing loss, frequent otitis, delayed bone age, and learning disorders. Normal laboratory tests. No renal and cardiologic malformations were found. She was treated with rhGH between 9.8 and 14 years old. Spontaneous pubertal development at 10.3 and menarche at 11.3 years old.
Results: Cytogenetic analysis of peripheral blood samples by G-banding revealed mosaicism 45,X[46]/47,XX,+21[4]. At age 22.7 she had an uneventful pregnancy, giving birth to a girl with 3.100g birth weight and normal chromosome constitution. She is now 3.6 years old. Height: 99.1cm(Pc35); Weight: 15.6 Kg(Pc55). Normal clinical features.
Conclusions: This is the first case of pregnancy in a patient with Down-Turner syndrome resulted in a healthy baby.

P1-d1-539 Puberty and Gonads 1

Benefit of testosterone in pediatric genital trauma

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Background: Pediatric genital trauma is an uncommon presentation to paediatric surgeons. Options for reconstruction to provide a functional phallus with erectile tissue are often limited. Two male children were referred for endocrine consideration of testosterone administration having sustained loss of penile tissue.
Case reports: Child 1 sustained substantial loss of erectile tissue, following circumcision for religious reasons, at age of 2 ½ months. Prior to treatment the length of penis was 1.5cm, with a width of 1.1cm at the base of the phallus. Administration of four injections (25mg) of intramuscular testosterone esters one month apart and topical testosterone to the area for two 1 month periods resulted in regrowth of almost all corpora cavernosa and part of the glans, giving 2cm of normal erectile tissue and a further 1cm of almost normal looking erectile tissue allowing later surgical reconstruction.
Child 2 sustained genital amputation including both testes and the majority of penile tissue, following a lawnmower accident at age 4 years. Multiple surgical attempts to preserve and re-implant penile tissue were unsuccessful, leaving only 0.8 x 1cm of viable tissue. Four intramuscular injections of 50mg testosterone enanthanate resulted in penile shaft regrowth to 2.5 x 1cm, allowing the prospect of future cosmetic correction.
Excessive skeletal advancement did not occur in either child.
Conclusion: In cases of genital trauma involving loss of penile tissue in childhood, a trial of low dose exogenous testosterone may result in the enhancement of any remaining erectile tissue without adverse effects on bone age or excessive linear growth. Not only is this important in terms of cosmetic

appearance but it provides options in terms of surgical achievement of a functional phallus. Regular clinical review to assess growth and tissue response is necessary to ensure that sufficient but not excessive testosterone is given.

P1-d1-540 Puberty and Gonads 1

Efficacy of the hyperinsulinaemia treatment with metformin on androgen plasma levels and early adolescence PCOS features in obese prepubertal females

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Background: Prepubertal females with severe obesity often show hyperinsulinemia (HI) and hyperandrogenemia associated with future PCOS features.
Objective: To evaluate efficacy of HI treatment with metformin vs lifestyle program alone on androgen plasma levels and future PCOS features in severely obese prepubertal females.
Methods: Sixty obese prepubertal females (8.5 ± 0.5 yr) have been studied. Insulin resistance (HOMA index) and HI were evaluated by glucose and insulin plasma at 0' and 120' of an oral glucose tolerance test. Basal and after ACTH test plasma androgen levels (free testosterone (fT), Δ4androstenedione (Δ4), 17OHP) were evaluated to exclude enzymatic adrenal defects. Thirty subjects were followed for 5 years (until menarche plus 2 years), under a lifestyle program (Group A) and 30 subjects with the same program plus metformin treatment (500 mg bid) (Group B). 2 groups were similar for BMI (+ 3.0 ± 0.5 SDS), basal (42.2 ± 5.2 μU/ml) and after glucose loading (341.2 ± 56.54 μU/ml) insulin levels, HOMA (9 ±2) and basal androgen levels (fT 4.2±1.2 pg/ml; Δ4 6.2± 1.3 nmol/L). A pelvic ultrasound (US) was performed at the end of the study. The hospital Etical Committee accepted the study and a written informed consent was obtained from children's parents for metformin use.
Results: At the end of the study BMI and androgen levels were significantly lower in group B vs A (BMI: 1 vs 2.5SDS, p< 0.001; fT: 1.2 vs 4.5, p < 0.0001; Δ4 2.8 vs 7.5, p< 0.0001). Age of menarche was lower in group A (10 vs 12 yrs) and amenorrhea > 1 month was significantly more frequent in group A (55%) vs B (8%). Pelvic US showed PCOS features in 45% of patients of group A vs 5% of B.
Conclusions: Hyperinsulinemia treatment with metformin is more efficacy than lifestyle program alone in persistent overweight decrease and androgens levels reduction in obese prepubertal females. Precocious normalization of androgen excess may prevent early evolution towards PCOS features.

P1-d2-541 Puberty and Gonads 2

The effect of *CYP21A2* heterozygous mutations on the values of DHEAS and other androgens in women with PCOS

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Background: Girls with premature adrenarche (PA) are more prone to develop PCOS than girls with timely occuring activation of the reticular zone. DHEAS, a marker of reticular zone activation is higher in PCOS women than in normal females. Molecular defects of the *CYP21A2* gene are more frequently identified in girls with PA than in controls.
Objective and hypotheses: To examine whether or not the presence of *CYP21A2* heterozygocity modifies the values of DHEAS and of other androgens in women with PCOS.
Subjects and methods: 197 women with PCOS, with (PCO+) or without (PCO-) abnormal ovarian morphology and 68 control women were studied. Women with basal and post ACTH 17OHprogesterone (17OHP) values greater than 2 and 10 ng/ml, respectively were excluded. Basal values of DHEAS, $\Delta_4$androstendione, 17OHP and testosterone (T) were determined by conventional techniques. Forteen molecular defects of *CYP21A2* gene were looked for by allele-specific PCR in all subjects.
Results: 19 heterozygotes were identified without difference in frequency between patients and controls. DHEAS was higher in PCOS women vs controls with no difference between PCO+ and PCO- groups, while the other androgens were higher in PCO+ compared to PCO- groups (Table).

	PCOS	Contols	p	PCO+	PCO-	p
DHEAS (ng/ml)	3340.6 ±1296.9	1808.9 ±777.1	0.001	3469.4 ±1311.4	3316.5 ±1295.6	0.430
Testosterone (ng/dl)	92.1 ±29.4	39.5 ±12.5	0.001	96.7 ±31.7	87.1 ±24.4	0.024
Δ $_4$A (ng/ml)	2.97 ±1.04	1.63 ±0.45	0.001	3.22 ±1.11	2.72 ±0.92	0.001
17OHP (ng/ml)	1.19 ±0.58	0.73 ±0.42	0.001	1.34 ±0.61	1.04 ±0.48	0.001

[Hormone values (Mean±SD)]

Heterozygous subjects had lower DHEAS values compared to PCOS subjects without heterozygosity (3394.6±1302.4 vs 2685.4±1058.9, **p:** 0.041), while all other androgens did not differ among these groups.
Conclusions: With the exception of DHEAS, androgenemia is not modified by the presence of *CY21A2* mutations in women with PCOS. The presence of PCO morphology does not affect DHEAS sulfate values whereas the other androgens are higher in the PCO+ group compared to PCO- one.

P1-d2-542 Puberty and Gonads 2

Abstract has been withdrawn

P1-d2-543 Puberty and Gonads 2

Evaluation of diagnostic criteria of polycystic ovary syndrome (PCOS) during adolescence

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Background: Different PCOS diagnostic criteria have been used in adult women, but whether these are appropriate for making this diagnosis during adolescence is controversial.
Objective: To study prevalence of biochemical hyperandrogenism (BH), polycystic ovarian morphology (PCOM) and different PCOS phenotypes in hirsute/oligomenorrheic adolescents and to determine cut-off levels of hormonal and ultrasonographic findings that differentiates PCOS from healthy girls.
Methods: We studied girls (N=30) with PCOS diagnosed based on NIH criteria (Ferriman score ≥ 7 and oligomenorrhea (OA): menses duration ≥ 45 days) and non-hirsute girls with regular menses (C, N=65).
Hormonal profile and ultrasonographic study were performed during follicular phase. BH was defined by testosterone (T) ≥0.6ng/ml and/or free androgen index (FAI) ≥4.5%, as previously reported by us in adult women. PCOM: defined by Rotterdam criteria. Data analysis: unpaired T test or X^2, ROC curve.
Results: BMI, T, FAI, inhibin b (INHB), ovarian volume (OV), follicular number (FN) were higher and SHBG was lower in PCOS than C. Age and anti-Müllerian hormone (AMH) levels were similar in both groups. BH, PCOM were more prevalent in PCOS than C (80% v/s 24.6%, and 96.7% v/s 35.3%, respectively, P< 0.0001). Phenotypes in PCOS group were: Hirsutism (H)+OA+BH+PCOM (76.7%); H+OA+PCOM without BH (20%), H+OA+BH without PCOM (3.3%). The best sensitivity/specificity, evaluated with ROC were: INHB ≥ 110.6 pmol/l (area under the curve (AUC)= 0.943),

FN ≥ 12.5 (AUC= 0.895), FAI ≥ 6.1% (AUC= 0.86), OV ≥ 9.7 ml (AUC= 0.851), T ≥ 0.69 ng/ml (AUC= 0.806). AMH had a poor discriminatory performance (AUC= 0.529).
Conclusions: Modified NIH criteria, with cycle length ≥ 45 days, are highly associated with BH and PCOM in adolescence. Cut-off points for hormonal, but not for ultrasonographic findings, are different to those previously reported in adults. AMH is of limited value for PCOS diagnosis in adolescents. FONDECYT Nº 1100123.

P1-d2-544 Puberty and Gonads 2

Gonadal impairment in children with acute lymphoblastic leukaemia treated by bone marrow transplantation: prevalence and risk factors

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Background: As the number of paediatric survivors of bone marrow transplantation (BMT) increases, it is becoming increasingly important to evaluate their late morbidity in order to improve their quality of life. Gonadal failure is a well-recognized late-complication of BMT in children with haematological malignancies which seems worth studying.
Objective and hypotheses: This study aimed to determine the prevalence and the potential risk factors of primary gonadal impairment in survivors of acute lymphoblastic leukemia (ALL) treated during childhood.
Methods: We carried out a retrospective study including 40 survivors of ALL (25 males, 15 females) aged 22.6 (11.3-31.7) years, who underwent BMT at mean age of 9.4 (2.3-17.3) years, using high-dose chemotherapy and hyperfractionated total body irradiation (TBI) in the period from 1989-2009 in one haematological centre.
Results: The prevalence of primary gonadal impairment was 83%. All females showed evidence of primary hypogonadism irrespective to pubertal status at the time of BMT, while 72% of males developed primary hypogonadism; the majority of them were at pubertal and post-pubertal stage at the time of BMT. All females experienced high FSH, and 87% of them had high LH at any time throughout the period of 5 years follow up post-BMT compared with only 60% of males had high FSH and only 16% had high LH. Both FSH/LH started to rise 6 months post-BMT in females at mean age of 11.7 (6.3-17.8) years, whereas in males, FSH started to rise 3 years post-BMT at average age of 14.2 (10.1-19.4) years, and LH after 5 years at average of 16.9 (14.8-19.8) years.
Conclusion: The prevalence of gonadal impairment is high in the patients with ALL who underwent BMT at childhood. This is probably owed to the highly intensive conditioning regimen. The onset of gonadotrophin elevation is earlier in females than males. Gender and age at BMT have been shown to be significantly associated with the risk of primary hypogonadism.

P1-d2-545 Puberty and Gonads 2

Anti-Müllerian hormone deficiency in female children and adolescents with congenital multiple pituitary hormone deficiency

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Background: Anti-Müllerian hormone (AMH) is often used to prognose a woman's fertility. It is mainly produced in the granulosa cells of preantral and small antral ovarian follicles and is believed to validly reflect the ovarian reserve. We assumed that the physiologic transient ovarian maturation during LH/FSH-induced mini-puberty might be essential for normal AMH serum levels in later life.
Objective and hypotheses: We aimed to asses the validity of AMH as fertility marker in female children and adolescents with multiple pituitary hormone deficiency (MPHD; deficiency of ≥ 2 axes). We speculated that they might be AMH deficient due to a total lack of the gonadotropins.
Methods: In a retrospective laboratory study we assessed AMH serum levels in females with congenital (n=20; mean age 13.9 years, range 0.7-27 years) or acquired (n=15; mean age 15.6 years, range 2-30 years) MPHD, in females with idiopathic hypogonadotropic hypogonadism (IHH; n=3; mean age 15.3 years, range 13-17 years) and in a control group (n=100; mean age 8.8 years, range 2 - 17 years) AMH was measured by ELISA (AMH Gen II ELISA ®, Beckman Coulter).
Results: In the control group, AMH ranged between 1.75 pmol/l (P3) and 67.8 pmol/l (P97). Almost all patients with congenital or acquired MPHD and IHH had AMH levels within P3 and P97. Remarkably, three patients with severe congenital MPHD were AMH deficient (0.1, 0.1 and 0.36 pmol/l AMH). For one of them we can proof missing mini-puberty (LH < 0.1 IU/l, FSH < 0.3 IU/l at an age of three weeks).
Conclusions: Females with a very severe congenital MPHD can be AMH deficient. This might be due to a missing transient ovarian maturation during mini-puberty. As they have presumably intact - but quiescent - ovaries, AMH is not a valid predictor of fertility in congenital MPHD.

P1-d2-546 Puberty and Gonads 2

Hormonal intervention in the management of adolescents with gender identity disorders (GID)

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Background: Since twenty years puberty suppression has generated a new, yet still controversial dimension to clinical management of GID.
Objective: Hormonal suppression of puberty, fully reversible, serves as a diagnostic aid, providing adolescent and therapist, time before more definitive decisions are made concerning (partially) irreversible steps of gender reassignment (cross sex hormones and surgeries).
Population and methods: From 1998 to 2010 54 MtF (male to female) and 73 FtM (female to male) received GnRHa as the first step which from the age of 16 years is combined with cross-sex hormones. Growth, metabolic aspects, bone mineral density (BMD) and clinical status were followed up.
Results: GnRHa delaying bone age, decreased height velocity. Oxandrolone in FtM and high dose estrogens in MtF, individually tailored, enabled manipulation of height to a more new sex- appropriate adult height.
On GnRHa BMI increased by about 6% with an increase in body fat, more in MtF than FtM. In neither sex insulin sensitivity decreased, whereas insulin growth factor-1 and sex steroids did in both sexes.
At start all had a normal BMD. During GnRHa BMD gradually increased in the younger patients, but slightly decreased in the relatively older adolescents. But during cross-sex hormones BMD caught up not different from increases in physiologic puberty. Remarkably, the highest BMD at the end of the treatment were seen in the patients who had started hormonal intervention at an early pubertal stage.
Suppression of puberty was well received, without any regret. Rather, many patients experienced the age of 16 to start with cross-sex hormones, determined by legal reasons, as too late.
Conclusion: Medical intervention in adolescents with GID appears to be safe and effective. Well-balanced persons with a longstanding diagnosis, may benefit from addition of cross-sex hormones to GnRHa earlier than 16, allowing experience of somatic pubertal changes at a more appropriate age.

P1-d2-547 Puberty and Gonads 2

Absence of functional TAC3 and TACR3 mutations in a cohort of patients affected by familial central precocious puberty

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Background: The genetic mechanisms involved in the early activation of GnRH secretion that is the source of central precocious puberty (CPP) are yet unknown. Ongoing studies intend to demonstrate that the neurokinin B (NKB) and its receptor (NK3R), also named tachikinin 3 (TAC3) and tachikinin 3 receptor (TACR3) play an active role in the regulation of the hypothalamic-pituitary-gonadal axis and thereby, also in the regulation and activation of puberty.
Recently it has been discovered that the loss-of-function mutations of the genes TAC3 and TACR3 - which respectively code the neurokinin B and its receptor - are engaged in the genetic genesis of Isolated Central Hypogonadism.
Objective: The aim of this study was to detect the presence of activating mutations with a gain-of-function of TAC3 and TACR3 genes in patients affected by familial CPP.
Methods: 14 patients (F, M) presenting with idiopathic CPP running in family, belonging to 7 different families have undergone the analysis by automated direct sequencing of entire coding region of the TAC3 and TACR3 genes.
Results: The result of this study showed the presence of a polymorphism c*73C>T in the gene TACR3 in 4/14 cases (28%), belonging to 3/7 families (42%). This polymorphism was present in the general population of the database of 1000 Genome Project. No other variants of the genes TAC3 and TACR3 were identified.
Conclusions: This is the first study conducted on genes TAC3 and TACR3 in CPP. We didn't identify causative TAC3 and TACR3 activating mutations in this cohort of patients. The polymorphism c*73C>T in the gene TACR3, found in 28% of the cases, do not seem to be associated with CPP. However, the data obtained need to be confirmed using a larger sample size and evaluating the time of the onset of puberty in those subjects of general population carrying this polymorphism.

P1-d2-548 Puberty and Gonads 2

New puberty growth model for estimation of individual pubertal growth parameters and their precision

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Background: Mathematical models for pubertal growth parameters giving individual precision is lacking.
Objective and hypotheses: A mathematical model can describe puberty variables mid puberty (P50%): peak height velocity (PHV), onset of puberty, end of puberty for which the precision can be described (confidence intervals=CI) for each individual.
Methods: From a model (QEPs model, Quadratic Exponential Puberty stop) we have evaluated the P(uberty) function, half area under the curve (AUC) as ageP50, and a mathematically calculated PHV of the total curve (ageTPHV) using one population from Gothenburg born 1974 (n=3655). A constructed variable "MathSelect" based on 9 parameters was developed for assessing the quality of data.
Results: In 1690 boys and 1665 girls with longitudinal data, usually once a year, the individual CI for age of ageP50 was typically within ± 0.2 to 0.3 year 50 % of the children had a CI ± 0.35 year. 20% had CI ± 0.25 year and 9% had CI ± 0.2 year. The MathSelect variable >1 was found useful for excluding children with low quality data. Exclusion of data during infancy/childhood, < 7 yrs, in a group with good pubertal data reduced the number of children to n=193 which could be evaluated with high precision. Besides available number of data points during infancy, childhood and puberty, the CI was influenced by the size of the pubertal height gain. The difference between ageTPHV and ageP50 (pure pubertal part of total growth curve) in the relation to the individual CI for ageP50 had a negative slope by age, more for girls than boys.
Conclusions: The mathematical model gives new information of pubertal growth with good individual precision. This improves computerized estimation of data quality and evaluation of influence of hormones, disease and environment on timing and amount of pubertal growth.

P1-d2-549 Puberty and Gonads 2

Idiopathic central precocious puberty (ICPP), adult lung function and asthma

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Background: Female idiopathic central precocious puberty (ICPP) is a rare disease characterized by the early onset of secondary sexual characteristics before 8 years of age. According to recent reports adult women with early menarche (< 11 years) have a lower lung function and a higher prevalence of asthma symptoms.
Objective: The aim of our study is to analyse the lung function and the incidence of asthma symptoms in young women with a history of ICPP treated during childhood with Gonadotropin Releasing Hormone agonist (Gn-Rha).
Methods: We compared 23 patients with a history of treated ICPP (mean age 18.7, range 14-27 years) and 20 healthy girls (mean age 21.8, range 14-26). All were evaluated using a questionnaire, spirometry pre and post β_2 agonist, impulse oscillometry and measurement of fractional exhaled nitric oxide (FeNo).
Results: 8,7% (N=2) of women with a history of ICPP had a significant reversibility of FEV_1 after β_2-agonist, in absence of asthma symptoms. Patients, non-smokers, had FEV1 (mean 103,5 vs 110,1; p=0,042), FEV1 post β_2-agonist (mean 107,1 vs 114,6; p=0,043), FEV1/FVC post β_2, (mean 107,1 vs 111,1; p=0,046), PEF (mean 93,9 vs 97,4; p=0,05) and MMEF (mean 90,2 vs 106,5; p=0,023) significantly lower than in healthy controls. Tiffeneau index and MMEF post β2-agonist correlate negatively with the hysterometry at diagnosis of ICPP ($p < 0.01$ and $p < 0.05$ respectively). There was a negative correlation between age at diagnosis of ICPP and pulmonary resistance. Unexpectedly FeNo was significantly lower in patients with pre-existing ICPP compared with healthy controls.
Conclusions: In our experience, girls treated for ICPP reach a lower lung function and develop a greater bronchial hyperreactivity in adulthood, despite treatment with Gn-Rha. As metabolic and hormonal factors seem to play an important role in achieving pulmonary health in adulthood, it would be useful the evaluation of spirometric parameters in new diagnosis and follow-up of ICPP.

P1-d2-550 Puberty and Gonads 2

Serum inhibin B, but not AMH or INSL3 levels, are helpful in discriminating between prepubertal boys with constitutional delay of growth and puberty (CDGP) and hypogonadotropic hypogonadism (HH)

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Background: In boys≥14 years of age, the differentiation between CDGP and a permanent developmental arrest is challenging. Diagnostic aids such as gonadotropin serum levels and various stimulation tests all have limitations in sensitivity and specificity. In CDGP mistakenly assigned as HH, hormonal replacement will suppress the pubertal activation of the gonadotropic axis. An unnecessary lifelong hormonal treatment may ensue. Sertoli cells are the most active cell population in the prepubertal testis, secreting Inhibin-B and

AMH. Inhibin-B increases, AMH declines during puberty. INSL3 is produced concomitantly to testosterone by Leydig cells.
Objective and hypotheses: To assess the diagnostic utility of Inhibin-B, AMH and INSL3 in male patients with delayed puberty in the differentiation between CDGP and HH.
Methods: Tanner stage, testicular volume, basal and GnRH-stimulated hormone levels and the sense of smell of 52 boys aged >14 years, referred for late puberty were assessed. Patients were grouped into 3 groups: n=15 boys with HH, n=9 prepubertal boys with CGDP and n=28 early pubertal boys with CDGP. The sera drawn at the time of the first referral were analysed for Inhibin-B, AMH and INSL3.
Results: Inhibin-B levels of HH-patients (median [± 95%CI]: 13,4[12,4-23,4] pg/ml) were significantly lower than those of prepubertal patients with CDGP (66,1[31,8-86,2] pg/ml; p=0.0028) and of early pubertal patients with CDGP (136,7[115,5-162] pg/ml); p< 0.0001). Receiver operating characteristics for diagnosis of CDGP vs. HH (Inhibin-B ≥29 pg/ml): sensitivity 95%, specificity 80%, positive predictive value 91 % (p< 0.001). Inhibin-B correlated with delta-LH during GnRH testing (R^2=0,44). INSL3 levels and AMH were not significantly different in the pre-pubertal CDGP group than in the HH group (p=0.69/0.33)
Conclusions: Inhibin-B, but neither AMH, nor INSL3 constitutes a biomarker to assess, whether a prepubertal boy with pubertal delay will enter puberty spontaneously or not.

P1-d2-551 Puberty and Gonads 2

Differentiation of olfactory placodal cells and their derivatives from human pluripotent stem cells

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Background: Preplacodal ectoderm develops at the anterior neural plate border region and gives rise to the cranial sensory placodes including the olfactory placode (OP), a proposed source of GnRH neurons. During embryonic development, GnRH neurons migrate from the OP to the hypothalamus where they control the function of the reproductive axis. Patients with Kallmann Syndrome (KS) display defective development and/or migration of GnRH neurons, which is clinically manifested as reproductive failure and decreased/absent sense of smell.
Objective and hypotheses: To understand the developmental mechanisms underlying KS, we have generated a differentiation protocol for OP and its derivatives by using human pluripotent stem cells.
Method: The protocol is based on known signaling cascades in the neural plate border region.
Results: In human embryonic stem cells (hESCs), modulation of three signaling pathways induced expression of several preplacodal and olfactory placodal markers such as *EYA2*, *DLX5*, *FOXG1* and *PAX6*, and markers of olfactory neurons *MASH1* and *OMP*. When the hESC derived OP-like cells were further differentiated towards GnRH neuron identity, a considerable increase in *GNRH1* expression was observed.
Conclusions: A detailed characterization of the prospective GnRH neurons by qPCR, immunocytochemistry, flow cytometry and electrophysiology is currently on-going. In the second phase of this project, the differentiation potential of KS patient-derived induced pluripotent stem cells into GnRH neurons and other OP derivatives will be modelled.

P1-d2-552 Puberty and Gonads 2

Urinary bisphenol A levels in Turkish girls with idiopathic central precocious puberty

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Background: Bisphenol A (BPA) is an industrial chemical which especially used in the structure of plastics and food packaging materials. BPA is suggested to have negative health effects on both laboratory animals and humans. The importance of BPA as an estrogenic endocrine disrupter has been increasing in regards to the recent decline in onset of puberty, particularly among girls.
Objective and hypotheses: In this study we aimed to determine the urinary BPA levels in idiopathic central precocious puberty (ICPP) cases.
Methods: Nonobese and newly diagnosed girls with ICPP (n=28, age=4-8 y) who were admitted to Akdeniz University Faculty of Medicine Department of Pediatrics between September 2010 - February 2012, constituted the study group. Control group comprised 25 healthy girls of comparable age with no history of ICPP and any other endocrinological disorder. Urinary BPA levels were measured by using high performance liquid chromatography.
Results: In ICPP group, urinary BPA levels were significantly higher compared to the control group [median 8,34 (0,84-67,35) µg/g creatinine and 1,62 (0,3-25,79) µg/g creatinine (p=0,001) (OR =8,68, 95% CI: 2,03-32,72, p=0,001) respectively]. There was no marked correlation between body mass index in both of the groups.
Besides, there was no significant correlation between urinary BPA levels and serum luteinizing hormone, follicle-stimulating hormone, and estradiol levels in ICPP group.
Conclusions: To our knowledge, this is the first study in the literature evaluating the urinary BPA levels in ICPP girls. We may postulate that estrogenic effects of BPA may be an etiologic factor in ICPP, although similar studies with a larger number of patients are needed to confirm the presented data.

P1-d3-553 Puberty and Gonads 3

Association analyses of CYP19A1 gene polymorphisms with central precocious puberty in girls

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Background: Precocious puberty is characterized by early activation of the pituitary gonadal axis. Estrogen is the final key factor to start onset of puberty. The cytochrome P450 19A1 (CYP19A1) gene encodes an aromatase that is responsible for the conversion of androgens to estrogen, which is key step in estrogen biosynthesis. The raised sensitivity of CYP19A1 gene, which may caused by mutation or polymorphism, has been mentioned for interpreting the etiology of precocious puberty.
However, currently there are a few studies regarding CYP19A1 gene mutations or polymorphisms.
The aim of this study is to identify CYP19A1 gene mutations or polymorphisms in girls with central precocious puberty (CPP).
Methods: 203 Korean girls with CPP were included in this study and 101 healthy Korean female adults as the control group. All coding exons of the CYP19A1 gene were sequenced. The relationship between identified sequence variations and CPP were evaluated via the comparison of allele frequencies between the two groups.
Results: Ten polymorphisms were identified in the CYP19A1 gene. Among the 10 polymorphisms in this study, 7 polymorphisms have been previously reported, whereas the other 3 were novel polymorphisms. Among the polymorphisms, only one known polymorphism in Exon 3 (51529112 A/G) was significantly more frequently detected in the patient group (P=0.039). We compared the clinical characteristics and hormone values among the three subgroups (the subgroup with 51529112 A/A, A/G, and G/G). Although 51529112 A/G was detected more frequently in the patient group, the three genotypes did not differ significantly in clinical parameters and laboratory values.

Conclusions: The polymorphism scanning and typing of CYP19A1 uncovered several potentially meaningful polymorphisms, but the conclusion was not solid and further supporting clinical evidences were not found in this study.

P1-d3-554 Puberty and Gonads 3

Thirty-six months treatment experience of two leuprolide acetate 3 month depot formulations for children with central precocious puberty

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Background: Short term efficacy and safety of leuprolide acetate (LA) 3 month (M) depot 11.25 or 30mg in children with central precocious puberty (CPP) has been demonstrated (Lee, et al. JCEM, 2012).
Objective and hypotheses: To assess long term (36M) hypothalamic-pituitary-gonadal axis suppression and safety of LA 3M depot 11.25 or 30mg in children with CPP.
Methods: 72 children (baseline mean age 8.5±1.6 yrs, 65 females) with CPP treated with 11.25 (N=34) or 30mg (N=38) 3M depot LA with continued LH suppression at 6M were followed for up to 36M of additional treatment. Peak stimulated LH< 4mIU/mL was considered suppressed, and physical exams assessed signs of puberty. Adverse events (AEs) data were collected.
Results: Suppression in peak stimulated LH and physical signs of puberty were assessed (Table). In the 11.25mg group, 5 subjects escaped LH suppression over 36M; 3 of 5 subjects were suppressed at their subsequent visit; 2 of 5 were considered failures at subsequent visits but had no evidence of progression in Tanner Staging. In the 30 mg group, 2 subjects escaped LH suppression, but were suppressed at the subsequent visit. AEs were comparable between groups with injection site pain being the most common AE (29.4% in 11.25mg and 23.7% in 30mg). One serious AE (VP shunt malfunction) occurred, and was not considered treatment related. None of the AEs led to discontinuation of study drug. The safety profile over 36M was similar to that previously reported.

	12M 11.25mg	24M 11.25mg	36M 11.25mg	12M 30mg	24M 30mg	36M 30mg
Peak Stim LH suppression (%,n/N)	90.3,28/31	87.5,14/16	77.8,7/9	96.9,31/32	100,18/18	100,11/11
Physical signs of puberty suppressed (%, n/N) Female	85.7,24/28	78.6,11/14	87.5,7/8	80.8,21/26	75.0,12/16	66.7,8/12
Male	100,1/1	100,1/1	0,0/0	60.0,3/5	33.3,1/3	100,1/1

[Table]

Conclusions: The 2 doses of LA 3M depot were associated with an acceptable safety profile and provided maintenance of LH suppression in children with CPP up to 36M or until readiness for puberty.

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Seasonality of menarche in normal weight and obese school children

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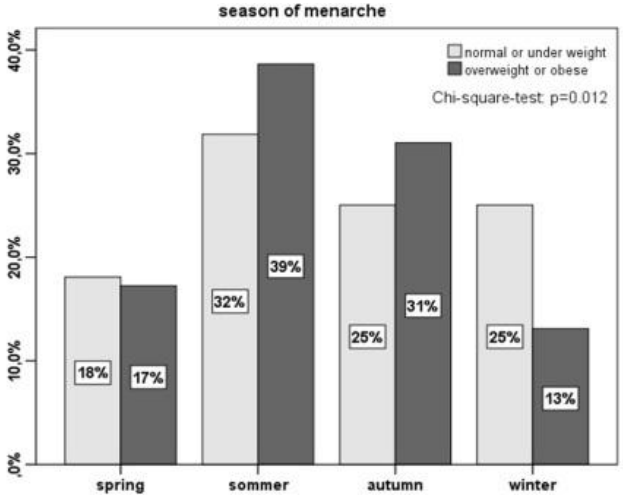
Background: The pivotal role of chronobiology in the regulation of metabolic parameters has gained large interest in last years. However, while seasonality plays a central role in the reproductive regulation in many species, so far seasonality of human menarche has only been investigated in very few cohorts.
Objective and hypotheses: The age at onset of menarche is inversely correlated to body weight. To analyze an additional effect of chronobiology on the onset of menarche, we have studied the monthly and seasonal distribution of menarche in a schoolgirl cohort, where we have already shown a correlation of body weight and menarche.
Methods: In a cross sectional study anthropometric data from 1840 healthy school girls (10-15 Ys.) were collected. 50% of the girls (n=937) were able to remember undoubtedly month and year of their first menstrual bleeding. The study cohort was divided into under- or normal weight girls (n=21; n=770; total n=791) and overweight or obese girls (n=145). The seasonal distribution of menarche was expressed in % in relation to these two weight categories.
Results: A significant seasonality of menarche was observed with an incidence maximum of 32.9% in summer and a minimum of 17.9% in spring. By further stratification concerning BMI, the seasonality remained significant.



[figure c]

Conclusions: We describe for the first time a strong seasonality of the onset of menarche in an European population of normal weight as well obese/overweight children. Therefore, the increase of daylight in spring and summer seems to still play a so far under-recognized role in human reproduction despite a more indoor lifestyle.

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Serum vascular endothelial growth factor-A (VEGF-A) levels in normal children and adolescents and precocious puberty girls

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Background: Vascular endothelial growth factor-A (VEGF-A) is essential for normal growth plate morphogenesis, including blood vessel invasion and cartilage remodeling. VEGF is expressed in the human pubertal growth plate and the VEGF protein level increases with pubertal progression in previous study. There are sexual differences in pubertal timing and proportions of adipose tissue.
Objective and hypotheses: The aim of this study was to assess the VEGF-A level according to pubertal stage by sex and investigate the relationship with precocious puberty.
Methods: Our sample included 153 normal children and adolescents (male; 92, female; 61) aged 6-15 years and 30 precocious puberty girls. VEGF-A, leptin, fasting glucose, insulin, lipids, sex hormone, gonadotropin level and bone age were analyzed according to pubertal stage and obesity. We measured serum level of VEGF-A using ELISA kit.
Results: Mean value of VEGF-A were similar between normal puberty boys and girls. In boys, VEGF-A level was not significantly different between prepuberty and puberty group (433.7 ± 326.1 pg/mL vs. 483.9 ± 390.5 pg/mL). In girls, VEGF-A level was significantly higher in puberty group than prepuberty group (596.0 ± 405.3 pg/mL vs. 264.2 ± 138.0 pg/mL, $P < 0.001$) and was significantly correlated with tanner stage ($r = 0.423$, $P = 0.001$), estradiol ($r = 0.443$, $P = 0.011$). VEGF-A level was significantly correlated with bone age advancement (male; $r = 0.345$, $P = 0.020$, female; $r = 0.355$, $P = 0.043$) but not

with BMI in both sex. VEGF-A level was significantly higher in precocious puberty girls than prepuberty girls with same chronological age.
Conclusions: Our study showed sexual differences in VEGF-A level according to pubertal stage. VEGF-A may be involved in the progression of precocious puberty girls. Further investigations related to pathophysiological mechanism of precocious puberty are needed.

P1-d3-557 Puberty and Gonads 3

Once-yearly histrelin subcutaneous implants provide continuous suppression of the hypothalamic-pituitary-gonadal axis for up to 6 years in children with central precocious puberty

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Background: Children with CPP often require several years of GnRHa therapy. An extended-access, open-label phase 3 study demonstrated that sequential once-yearly subcutaneous histrelin implants (Supprelin LA) suppress the HPG axis through 4 years. However, no study has reported on the use of histrelin for more than 4 years in CPP patients.
Objective: To report phase 3 long-term extension data through 5 and 6 consecutive years of histrelin therapy.
Methods: Patients who received a fifth histrelin implant were included in this analysis. GnRHa-stimulated (peak) luteinizing hormone (LH), peak follicle-stimulating hormone (FSH), and basal estradiol levels were measured. Auxology outcomes including bone age/chronological age (BA/CA) ratio and Bayley-Pinneau-predicted adult height (PAH) were assessed. AEs were recorded.
Results: Eleven children (10 girls; mean age at baseline [time of first implant] 6.4 years [range, 4.5-9.1 years]) were included; 3 had received prior GnRHa therapy. After 5 years of histrelin: peak LH (0.37 vs 15.73 mIU/mL; *P*=.026) and FSH levels (1.91 vs 12.77 mIU/mL; *P*=.006) continued to be significantly suppressed compared with baseline; mean BA/CA ratio was significantly lower (1.11 vs 1.40; *P*=.006); and PAH was significantly higher (167.50 vs 150.88 cm; *P*=.003). Only 1 girl had an estradiol level >20 pg/mL (prespecified suppression) throughout 5 years of treatment. Two girls received a sixth implant; peak LH and FSH levels remained suppressed through 6 years compared with baseline. Most frequently reported treatment-related AE for patients receiving at least 5 implants was mild/moderate implant site reaction (7 AEs in 5 [45%] patients); 5 of the 7 AEs occurred within 1 day of implant (1 patient reported site pain 4 days after implant and 1 patient reported site pain 4 months after implant).
Conclusion: Up to 6 years of continuous histrelin implant therapy is effective in suppressing the HPG axis and improving auxologic outcomes in patients with CPP.

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New puberty growth model for estimation of age for peak height velocity compared with a manual method

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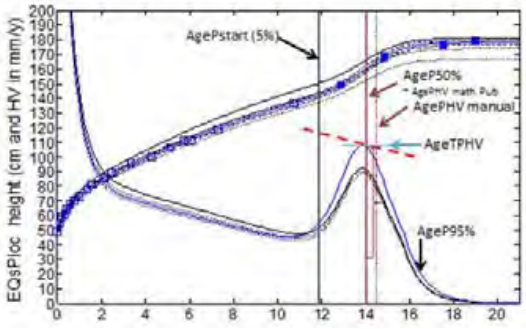
Background: There is a lack of methods describing pubertal growth in a computerized way.
Objective and hypotheses: To compare a mathematical model, describing pubertal growth, for age at start P5%, mid P50% and end P95% of pubertal growth and total curve peak height velocity (TPHV) to compare with manually identified PHV.
Methods: From a new growth model (QEPs Quadratic Exponential Puberty stop) we used the P(uberty) function for estimating PO (5% of P(AUC), mid puberty as P50% and PE (95% of P(AUC)). The calculated PHV from total growth curve (TPHV) was compared with the manually identified PHV (against a ICP based grid) . The Swedish growth reference, born 1974 (n=3655 of which 2622) was selected.
Results: For the 1320 boys mean (SD) of ageP50% was 13.82 (0.96), ageTPHV 13.67 (0.97) and age at PHV 13.85 (1.00). For the 1302 girls mean (SD) of ageP50% was 12.08 (0.97), ageTPH 11.81 (0.99) and age at PHV 11.93 (0.95). PO, as P5% for boys was 11.77 (1.00) and for girls 9.80 (1.04). PE, as P95% for boys was 16.16 (0.99) and for girls 14.70 (0.97) giving a mean duration for boys of 4.8 years and 4.9 years for girls. The mean age difference between PHV and TPHV was for boys 0.18 (0.38) and for girls 0.11 (0.48). The mean difference between PHV and P50% was for boys 0.03 (0.38) and for girls -0.15 (0.48).
Conclusions: This new puberty growth model gives computerized information of start, mid and end of pubertal growth as well as the age at TPHV. This makes possible a better evaluation of influence of hormones, disease and environment on timing of amount of pubertal growth.



[Figure 1 AgeP05% (AgePstart 5%)=11.82, AgeTPHV=13.72, Pub=AgeP50%=13.87. AgePHV manual=13.89 AgeP95%=14.7]

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Different patterns of pubertal growth in girls with different pathways through puberty (pubarche pathway vs thelarche pathway)

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Background: Pubic hair appearing without breast development as the initiation of onset of puberty may be a manifestation of adrenarche or premature adrenarche. Pathways entering puberty may have impacts on the pubertal growth pattern.
Objective and hypotheses: To investigate the pubertal growth, final adult height(FAH) and body mass index(BMI) in girls who began puberty with pubarche pathway compared to those began with thelarche pathway.
Methods: 320 schoolgirls, recruited at age of 7.24±0.38 years (6.25 to 8.83 yrs), were followed up annually for 9 years (from 1992 to 2001). Anthropometric differences in 56 girls who entered puberty with pubarche pathway were compared with another 56 girls with thelarche pathway. 2 groups matched in age at onset of puberty, birth weight, birth length, target height(THt) and urban.
Results: No significant differences of height and BMI at onset of puberty were found between groups (134.41±5.72cm vs 134.40±5.12 cm, p>0.1, -0.09±0.85SDS vs -0.12±0.95 SDS, p>0.1), (16.58±15.81,p>0.1).
Age at menarche was similar between groups (12.98±1.27yrs vs 12.62±1.20yrs, p>0.1). Girls with pubarche pathway had increased peak height velocity(PHV) (8.41±1.22 cm vs 7.90±1.10 cm, p=0.023), but had shorter duration of pubertal growth(from initiation of puberty to FAH) (3.64±0.74yrs vs 3.99±0.85yrs, p=0.024), less total height gain during PHV and during pubertal growth (16.57±4.06 cm vs 18.67±4.15cm, p=0.009), (23.83±4.44cm vs 25.97±3.90cm,p=0.009), and had lower FAH, FAHSDS for THt (158.12±6.19cm vs 160.51±4.98cm, p=0.029), (-0.03±1.13SDS vs 0.40±0.91SDS,p=0.013). Girls with "pubarche" pathway also had increased

BMI than those with "thelarche" pathway when reached FAH(19.32±2.77 vs 22.45±3.16, p=0.029).
Conclusions: Girls enter puberty through the pubarche pathway had shorter duration of puberty, less pubertal growth and lower FAH, but greater BMI than those who enter through thelarche pathway.

P1-d3-560 Puberty and Gonads 3

Leptin during treatment of precocious puberty with GnRH-analogue or a combination of GnRH-analogue and growth hormone

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Background: Nutritional status is a regulatory factor for onset of puberty. A critical level of leptin, reflecting adipose tissue, may be necessary for the start and progression of puberty. The level of leptin has been shown to be inversely related to menarche. Treatment of precocious puberty with GnRH-analogue (GnRHa) may be associated with weight gain, but does not change leptin levels, which correlate with body mass index (BMI) and body weight. Since a decrease of growth velocity may occur following GnRHa-administration, addition of growth hormone (GH) to the treatment has been tried.
Objective: To study the effect of treatment with a combination of GnRHa and GH on levels of leptin in girls with precocious puberty in comparison with only GnRHa. GH would be expected to decrease fat mass, in turn reducing levels of leptin.
Patients: Forty-six adopted girls from developing countries with precocious puberty, 6-9 years old, were randomized to treatment with GnRHa or GnRHa+GH. Serum levels of leptin were analysed before and during 3 years of treatment.
Results: There was an overall increase of BMI, BMI-SDS as well as serum leptin during the study period. The two treatment groups did not differ with respect to these variables. Leptin and BMI were strongly correlated at all visits, $p < 0.001$. The change of leptin correlated positively with changes of BMI and BMI-SDS from 12 months and there was no difference between the treatment groups.
Conclusions: The increase of BMI-SDS during three years of GnRHa-treatment indicated a gradual increase of fat mass. The addition of growth hormone did not change this pattern, which is in line with the parallel increase of serum leptin in the treatment groups. The finding contrasts with earlier data demonstrating that growth hormone treatment of children decreases leptin either by increased lipolysis or by a direct effect on metabolism of leptin. Thus, the question emerges whether treatment with GnRHa may alter metabolic effects of GH.

P1-d3-561 Puberty and Gonads 3

Idiopathic central precocious puberty (ICPP) and maternal attachment security

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Background: Life-history theorie of early programming of human reproductive strategy stipulates that early rearing experience, including that reflected in infant-parent attachment security, regulates psycological, behavioral and reproductive development. Results revealed that individuals who had been insecure infants initiated and completed pubertal development earlier compared with individuals who had been secure infants.
Objective: The aim of our study is to assess maternal attachment styles in adult patients with a history of treated ICPP, compared to healthy control group, and to consider how the degree of security-insecurity of this relationship may predict pubertal development.
Methods: We selected 15 patients with a history of ICPP (range 14-24 years) and a control group of 15 healthy girls (range 14-26 years). The attachment style and separation anxiety of all these subjects were tested with Separation Anxiety Test (SAT), a semi-projective test for images, in the version modified by Grazia Attili.
Results: 53,3% (N=8) of patients treated for ICPP had a secure attachment style, 26.7% (N=4) had an insecure-avoidant attachment and 20% (N=3) insecure-ambivalent attachment. Of the 15 healthy controls, 66.7% (N=10) had a secure attachment, 26.7% (N=4) insecure-avoidant and 6.6% (N=1) insecure-ambivalent. Girls with a history of ICPP exhibit a maternal attachment definitely more insecure compared to girls with normal pubertal development (47% vs 33%).
Conclusions: These results showed that girls with a history of ICPP have maternal attachment style generally more insecure than the healthy population. Our data, despite the small size of sample, support a conditional-adaptational view of individual differences in attachment security and raise questions about the role of the maternal care, the quality experience of detachment and the rapprochement act during the first months of life on the biological mechanisms responsible for the precocious pubertal development.

P1-d3-562 Puberty and Gonads 3

Usefulness of basal serum LH in the diagnosis of central precocious puberty

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Background: It has recently been published that basal serum luteinizing hormone (LH) may be useful to differentiate central precocious puberty (CPP) from precocious telarche (PT). Nevertheless, controversy exists on the cut-off value to be used to distinguish between both entities.
Objective: The aim of the study was to determine the usefulness of basal serum LH to diagnose CPP in girls with PT.
Methods: 46 girls with PT were enrolled in the study. Chronological age was 7.35±0.82 years and time of follow-up at least 6 months after GnRH test. At the beginning of the study, post-GnRH-test serum LH values were considered in order to differentiate PT (Gr1 n=28 LH peak < 5 mIU/ml) from CPP (Gr 2 n: 18 LH peak >5mIU/ml). None of the patients included in Gr1 progressed to CPP in the 6 months following GnRH Test. Basal serum gonadotropins were measured using CMIA (Architec i2000 - Abbott).
Results: Basal serum LH in Gr1 (x± SDS: 0.12±0.06IU/ml, r: 0.06- 0.35) was significantly lower than in Gr2 (x± SDS 0.7±1.15IU/ml, r: 0.07-4) $p < 0.001$. ROC analysis showed positive predictive value was 81.5% and negative predictive value was 27.7%, accounting for a sensitivity of 81.5% and a specificity of 72.2%. In Gr1 35.7% of the patients had basal serum LH higher than 0.11mIU while 27% of those in Gr2 had basal serum LH lower than 0.11mIU/ml. (FISHER TEST p:0.016).
Conclusions: These results confirm that when basal serum LH is lower than 0.11mIU/ml it does not allow to differentiate between PT and CPP, similar findings have recently been reported by Pasternak et al (EJE, 2012).

P1-d3-563 Puberty and Gonads 3

Usefulness of a basal LH level to diagnose central precocious puberty (CPP) in girls

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Background: The diagnosis of CPP in girls requires gonadotropin stimulation test to confirm the hypothalamic-pituitary-ovarian axis activation. However,new and more sensitive immunoassays could be useful to achieve an acceptable diagnostic efficiency by means of basal serum gonadotropins levels.
Objective: To determine the usefulness of basal serum gonadotropins in the diagnosis of CPP in girls, using an electrochemiluminescense assay (ECLIA).
Methods: A cohort of 142 girls who presented breast development before 8 years of age who underwent GnRH stimulation test were included. Diagnosis of CPP was made on the basis of clinical criteria and a peak LH >6 IU/L. CPP girls with previous central nervous system condition or pathologic MRI were classified as neurogenic CPP (NCPP), the others were considered as idiopathic CPP (ICPP).

Girls who had lower peak LH values and showed no pubertal progression throughout follow-up for at least one year after the test were considered as premature thelarche (PT). Basal gonadotropins were analyzed by ROC curves to determine the best cut-off to differentiate CPP vs PT and their positive predictive value (PPV) and negative predictive value (NPV).
Results: 105 girls were classified as CPP (72 ICPP, 33 NCPP) and 37 as PT. ROC curves showed that a cut-off value of basal LH= 0.3 IU/L, setting the specificity (E) at 100%, had 64.42% of Sensitivity (S) in the whole group for the diagnosis of CPP, with a PPV of 100% and NPV of 50%. A basal LH value >0.3 IU/L identified 38/72 ICPP girls (S:52.8%) but identified 30/32 NCPP girls (S:94%, NPV:95%). Basal FSH >4.2 IU/L setting E at 100% showed S of 45% in the whole group.
Conclusions: Basal LH >0.3 IU/L using ECLIA is adequate to confirm CPP, however lower values are not definite to refute the diagnosis of CPP. Basal FSH does not improve diagnosis sensitivity. But in patients suspected of having NCPP, the basal LH value has high diagnostic accuracy for diagnosing CPP without requiring a further test.

P1-d3-564 Puberty and Gonads 3

Biological reference intervals for serum estradiol and testosterone in children

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Background: Specific and sensitive assays for estradiol and testosterone determinations are needed in clinical practice for evaluation of pubertal disorders and sex hormone replacement therapy in children. It has been proposed that the best prospect for determination of sex steroids lies in extraction and chromatography followed by mass spectrometry (MS).
However, some extraction RIA for determination of estradiol and RIA for determination of testosterone have the same sensitivity and specificity as the most sensitive MS.
Objective and hypotheses: To present our expanded pediatric reference intervals in percentiles in relation to their pubertal development.
Methods: Samples were collected from 66 girls and 88 boys, taken every 4th hours for 24 hours, starting at 0800h or 1000 h. Serum estradiol concentrations were determined by an extraction RIA (Spectria® Estradiol RIA, Orion Diagnostica). The lower limit of detection was 4 pmol/L (1 pg/ml). The interassay CV was 19% at 6 pmol/L and below 10% for levels above 70 pmol/L. Serum testosterone concentrations were determined using a modified RIA (Spectria testosterone; Orion Diagnostica). The lower limit of detection was 0,03 nmol/L (0,9 ng/dL). The interassay CV 20% at 0,1 nmol/L and less than 7% for levels above 0,9 nmol/L.
Results: Serum estradiol and testosterone concentrations increased throughout pubertal development. In girls, the estradiol peak value occurred at 0800 or 1000 h. For boys, the testosterone peak value occurred at 0600 or 0800 h.

		Serum estradiol levels (pmol/L), 5th-95th percentiles				Serum testosterone levels (nmol/L), 5th-95th percentiles
Pubertal stages in girls (breast according to Tanner)	n	0600 h	0800-1000 h	Pubertal stages in boys	n	0600-0800 h	1000 h
Pre (B1)	22	<4-21	<4-24	Pre (testis 1-2 mL)	31	0,1-0,46	0,04-0,46
Early (B2)	19	5-67	7-77	Early (testis 3-6 mL)	22	0,37-3,2	0,26-1,4
Mid-puberty, pre menarche (B3-4)	25	35-238	46-296	Mid-puberty (testis 8-12 mL)	21	2,3-17,0	1,65-10,7
				Late puberty (testis 15-25 mL)	14	9,9-25,9	6,3-20,7

[Morning reference intervals for children]

Conclusions: These RIA methods have the accuracy required for determination of sex steroids in children. Clinically useful reference intervals were established.

P1-d3-564b Puberty and Gonads 3

Fertility screening in men with acquired undescended testes: a long-term follow-up study

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Background: Undescended testis (UDT) may be of congenital or acquired origin. Congenital UDT (CUDT) carry risk of fertility problems later in life. Little is known about fertility and acquired UDT (AUDT).
Objective: Evaluation of testicular function in men with previously AUDT in whom spontaneous descent was awaited until puberty followed by orchiopexy in case of non-descent.
Methods: In 65 men with previously AUDT (unilateral N=50), of whom 33 men needed orchiopexy, andrological evaluation was performed, including medical history, physical examination, scrotal ultrasound, reproductive hormones, and semen analysis. Men with AUDT were compared with healthy controls (N=53) and men with CUDT (N=62, unilateral N=55).

Values are expressed as median (range) or number (percent).	Unilateral Acquired UDT group	Control group	Unilateral Congenital UDT group
Succesfull attempt to fatherhood	7 (70)	25 (86)	6 (55)
Normal testicular consistency	37 (74)	53 (100)[b]	29 (53)[a]
Testis volume (UDT)(ml)	9.3 (0.3-23.2)	15.8 (8.1-27.0)[d]	9.6 (2.7-22.9)
LH (IU/l)	3.7 (1.1-14.4)	3.6 (1.3-7.3)	3.3 (1.1-10.3)
FSH (IU/l)	5.5 (1.2-27.9)	4.5 (1.6-13.9)	4.8 (0.7-21.2)
Testosterone (nmol/l)	16.7 (6.6-37.0)	15.4 (7.6-34.7)	14.9 (8.2-28.7)
Inhibin B (ng/l)	161.0 (10.0-345.0)	168.0 (96.0-488.0)	157.0 (22.0-554.0)
Semen Concentration (10*6/ml)	20.0 (0-205.0)	54.5 (0.1-213.0) [d]	21.0 (0.1-276.0)
Progressive motility (%)	42.0 (3-75)	52.0 (9-91)[c]	41.0 (0-69)

[AUDT compared with controls and CUDT]

Results: Table 1 shows data of men with unilateral AUDT in comparison with controls and men with unilateral CUDT (Fisher's exact test:[a]P< 0.05;[b]P< 0.01;Mann-Whitney test:[c]P< 0.05;[d]P< 0.01). Men with bilateral AUDT in comparison with controls had significantly less often successful attempts to fatherhood, more often abnormal testicular consistency, smaller testicular volume, higher LH and FSH, lower Inhibin B, lower sperm concentration, and less motile sperm. No differences were found between men with bilateral AUDT and bilateral CUDT.
Conclusions: Fertility potential in men with AUDT was less than that in healthy controls. No differences could be found between men with AUDT and men with CUDT, except for more often a normal testicular consistency in men with unilateral AUDT.

P1-d1-565 Sex Differentiation 1

Cardiovascular monitoring with echo and MRI during spontaneous and assisted pregnancy in Turner syndrome

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Background: In Turner Syndrome (TS) pregnancy is a rare event and it is a major risk factor for aortic dissection, during pregnancy and after (2% or higher). Literature reports that the risk of death is increased 100-fold more than the general population.
Objective and hypotheses: To evaluate cardiovascular complications in TS during pregnancy.
Methods: 8/174 (4.5%) of our adult TS patients gave birth to 10 children (2 sets of twins) at a mean age of 28.75±7.75 yrs. 4 women had spontane-

ous pregnancies and 4 after assisted reproductive technology. 6 patients had X-mosaicism and 2 X-structural abnormalities. We monitored aorta dimensions during and after pregnancy, by echo and MRI. Published reference values were used to define each aortic segment as being dilated or not: sinuses of Valsalva 1.9 cm/m^2, Sino-tubular-junction (STJ) 1.6 cm/m^2, ascending aorta 2.0 cm/m^2.
Results: Before pregnancy, 3 TS had normal diameters, 5 had aortic dimensions (sinuses, STJ) within upper normal limits. Blood pressure was normal in all patients. 7 did not change during and after pregnancy and one dilated during pregnancy; she was monitored with echo at the beginning and during pregnancy. At sinuses of Valsalva the aortic diameters were (27 yrs) 2.07 cm/m^2 at the beginning of pregnancy and during-pregnancy at the 26th and 34th week of gestational age 2.15 cm/m^2. Thoracic MRI (26th week) confirmed the mild dilation. No increase of diameters was found until the end of pregnancy. She was submitted to an elective C section and gave birth to a normal female.
Conclusions: Spontaneous or assisted pregnancy in TS should be undertaken only after a cardiologic evaluation with cardiac echo and MRI to identify women at particular risk of cardiovascular complications during pregnancy. During pregnancy, echocardiography should be performed every 3 months to exclude aortic dilation, in particular between 16-20 weeks and blood pressure monitoring is mandatory.

P1-d1-566 Sex Differentiation 1

Blood cell chimerism in dizygotic twins following *in vitro* fertilization

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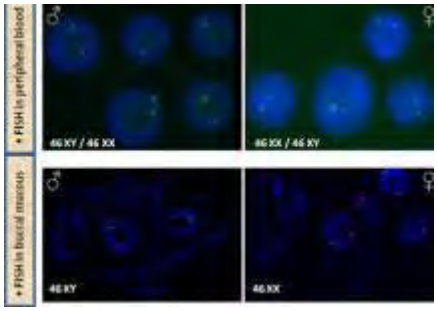
Background: An increased rate of twin pregnancies, usually dizygotic (DZ), is an effect of *in vitro* fertilization (IVF). Chimerism in dizygotic twins can be due to placental vascular anastomoses causing reciprocal hematopoietic stem cell colonization of bone marrow or to trophoblast cell admixture during early blastocyst development. We present a case of hematopoietic chimerism in dizygotic twins.
Case study: Twins (male and female) conceived by IVF were born after normal gestation at term (38 weeks). No physical abnormality was detected. At age 8 years a karyotype in blood was done in the female due to clitoromegaly. In 100 metaphases studied, two different lines: 46,XX (53%) and 46,XY (47%) were found and FISH studies confirmed the presence of the *SRY* gene in the 46,XY cells. A karyotyope in the male also revealed two different lines: 46,XY (58%) and 46,XY (42%) with *SRY* gene present in the 46,XY cells. Microsatellite analyses from blood DNA revealed tetraallelic contribution at some autosomal loci with similar proportion of maternal and paternal alleles and X/Y chromosome dosages suggestive of identical proportion of chimeric nucleated blood cells. FISH was performed with *X/Y* probes in buccal mucous: in all cells studied the female was 46,XX, and the male 46,XY (see Figure).



[Karyotype in blood and FISH in buccal mucous]

Conclusions: Blood from both twins revealed 2 equilibrated XX and XY cell populations, but buccal smears revealed homogeneous XX or XY cell population. Genetic analyses revealed chimeric lymphoid and myeloid cells in dizygotic twins, but no tissue mosaicism was detected, indicating that twin-twin transfusion syndrome is the most likely cause leading to chimerism and mutual immune tolerance.

P1-d1-567 Sex Differentiation 1

Pseudoautosomal region abnormalities in patients with Y-chromosome terminal AZFb+c deletions

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Background: Recent evidence indicates that infertile men with microdeletions of the Y chromosome (Y-D) may harbor abnormalities in the number of pseudoautosomal region (PAR) gene copies, which may affect the *SHOX* gene (PAR1) involved in long-bone growth, or the *ASMT* (PAR1), *VAMP7* (PAR2) and *ILR9* (PAR2) genes, which are associated with psychiatric diseases.
Objective: To study PAR1 and PAR2 in patients with a diagnosis of Y-chromosome classical AZF-deletions, and to analyze their longitudinal growth and neuropsychological development.
Hypothesis: Patients with Y-MD have an increased prevalence of PARs aberrations associated with abnormal stature and/or neuropsychological disabilities.
Methods: We studied 22 patients (1 child and 21 adult men), who were diagnosed with Y-MD (14 AZFc, 4 AZFb+c and 4 terminal AZFb+c) by the Multiplex Ligation-dependent Probe Amplification MLPA Kit P018-F1-SHOX to search for PAR gene copy variations. All subjects had a normal conventional karyotype.
Results: Only those patients with terminal AZFb+c Y-MD had PAR abnormalities. In agreement with their terminal Y-MD, these patients had only one copy of PAR2. Regarding PAR1, 2 patients had a loss, and 2 patients a gain of one copy. Of these patients, 2 had a history of learning disabilities and 3 had a diagnosis of mood disorders; 2 major depressive disorders (with one or three copies of PAR1) and 1 bipolar disorder (with one copy of PAR1). Furthermore, both patients with PAR1 deletion had growth disorders, one with severe short stature (Z score for height: -2.89) and one with very tall stature (Z score for height: +2.58).
Conclusions: Patients with terminal AZFb+c Y-deletions may have additional sex-chromosomal abnormalities, which include PARs. Therefore, in addition to their fertility problems, these patients must be evaluated for possible growth disorders, learning disabilities and/or psychiatric dysfunction.
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P1-d1-568 Sex Differentiation 1

Low expression of X-linked inhibitor of apoptosis (XIAP) in Turner syndrome patients with bicuspid aortic valves (BAV): possible role of apoptosis

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Background: Cellular apoptosis is a normal process occurring during embryogenesis. It is regulated by complex pathways and is involved in development of many organs, including the heart, kidneys, and inner ear. X linked inhibitor of apoptosis (XIAP) is the most potent human inhibitor of apoptosis (IAP) currently identified and abnormal expression in Turner Syndrome (TS) could explain some of the clinical features.

Hypotheses: Reduced XIAP expression may cause dysregulated apoptosis and be an underlying mechanism for some manifestations of Turner syndrome (TS), such as ovarian failure, congenital cardiac malformations and autoimmune diseases.
Objective: To analyze expression of XIAP mRNA in peripheral blood mononuclear cells (PBMCs) from patients with TS and assess its levels in relation to phenotypic features.
Methods: Ninety eight patients with TS (median age 19 years, range 1-68 years) were studied. Clinical, laboratory and imaging findings were extracted from medical records. XIAP expression was studied by real time quantitative PCR performed on cDNA, synthesized by reverse transcription of RNA extracted from blood leucocytes.
Results: Expression of XIAP was significantly less in patients with bicuspid aortic valves (BAV) (n=13) than those without (log XIAP -1.17±0.33 vs. -0.94±0.22, p=0.002). When analyzed for karyotype, only patients with BAV and mosaic karyotype had significantly low expression of XIAP (p= 0.006). There was no correlation between XIAP expression and other manifestations of TS (table 1). External phenotypic features significantly associated with BAV were shield chest, web neck, short neck, low hair line and multiple naevi. Patients with BAV had significantly higher incidence of coarctation of aorta (38.5 % Vs 5.9 % in those without BAV, p< 0.001).
Conclusions: Low expression of XIAP leading to increased apoptosis may be an underlying mechanism in BAV. However XIAP expression alone does not explain all the somatic and visceral stigmata of TS.

P1-d1-569 Sex Differentiation 1

The prevalence of neoplasm in Turner syndrome

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Background: Turner syndrome (TS) is a genetic syndrome caused by complete or partial absence of an X chromosome. It is the most common diagnosed sex chromosome abnormality in women, affecting 1/2000-2500 female live births. Mortality in women with Turner syndrome is 3-fold higher than in the general population, is raised for almost all major causes of death, and at all ages with the greatest excess mortality in older adulthood. The risk of cancer in patients with TS has been suggested but little studied.
Patients: We retrospectively reviewed the prevalence of tumors in our cohort of 85 women (mean age 27.05±11.17 yrs) diagnosed with Turner syndrome who attended at the Endocrinological Unit of our Department. Karyotype was 45,X in 45 and structurally abnormal X chromosome or X-mosaicism in 40 girls. During follow-up, 62 girls (72.9%) had been treated with growth hormone (GH), 64 (75.3%) with oestroprogestin and 20 (23.5%) with L-thyroxine.
Results: A total of 9 neoplasms (10.6%) were noted, in particular 2 CNS tumors (2.3%), 1 meningeal tumor (1.1%), 1 non melanoma cutaneuos neoplasm (1.1%), 1 hepatocarcinoma (1.1%), 1 pancreatic cancer (1.1%), 1 ovarian gonadoblastoma in a girl with a Y-chromosome lineage (1.1%), 1 breast tumor (1.1%), 1 thyroid cancer (1.1%).
Of the patient with neoplasms 5/9 (55%) had karyotype 45,X (p=ns). The average age at the diagnosis of tumor was 27.5 yr (range 8-43); in 3 (33%) patient the tumours occurred under the age of 18 yr (mean 12±4 yr). The presence of the tumors was not influenced by treatments.
Conclusion: The risk of cancer in patients with TS is not fully elucidated. In our cohort of TS the prevalence of neoplasm is similar to that expected in the general population. Even if the role of genes and hormonal drugs in the development of the tumors is discussed, in our retrospective review no correlation between genetic make up, treatment and neoplasm was found.

P1-d1-570 Sex Differentiation 1

Gonadoblastoma and dysgerminoma in girls with Turner syndrome and Y chromosome material: a single center experience

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Introduction: Cytogenetic analysis from peripheral lymphocytes detects Y chromosome mosaicism in approximately 6-12% Turner Syndrome (TS) patients (pts). Since the presence of Y chromosome material is associated with a 12-27% risk of developing gonadoblastoma and gonadoblastomas may transform into malignant germ cell neoplasms prophylactic gonadectomy is recommended in these pts.
Case study: We report on the incidence of gonadoblastomas and dysgerminomas in our series of 62 TS pts. In 5 pts (8%) Y chromosome material was found with the following karyotypes: Pt 1: 45,X/46,Y dic (Y), Pt 2: 45,X/46,XY. nuc ish (DXZ1x1,DYZ3x0), Pt 3: 45,X/47,XY +8, Pt 4: 46,X, der (X) t (i(X) (q10);Yq11), Pt 5: 45,X/46X idic (Y) (q12)/47,X idic (Y) (q12), idic (Y). Mean age at gonadectomy was 7.5 years (range 4.5-13.9). Pt 1 showed a left monolateral gonadoblastoma. Pt 2 had a gonadoblastoma on the left side and a gonadoblastoma transforming into dysgerminoma on the other side. Pt 3 to 5 had bilateral streak gonads without gonadoblastomas. In Pt 2 molecular cytogenetic analysis was also performed on the gonadal tissue. The Y chromosome prevalence was lower in the gonads than in the blood (20-27% vs. 90%).
Conclusions: Although data of only 62 pts were available the incidence of Y chromosome material and gonadoblastomas were identical in comparison to the literature (8% and 20%, respectively). In our series the karyotype of peripheral lymphocytes did not predict the tumor risk. Whilst we do not understand the process of malignant transformation of gonadoblastoma to dysgerminoma prophylactic gonadectomy remains the procedure of choice for TS pts with identified Y chromosome material and should be performed as early as possible.

P1-d1-571 Sex Differentiation 1

Y-chromosome mosaicism in Turner syndrome: body proportions and final height reached with GH-therapy

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Background: Short stature with abnormal body proportions (relatively short lower extremities and broad shoulders) is characteristic of Turner syndrome (TS). In these subjects GH-therapy improves final height (FH) and moderately modifies body proportions.
Objective and hypotheses: The aim of our study was to evaluate the effect of GH therapy on TS pts according to the presence of Y-chromosome material.
Methods: Anthropometric measurement (length and width), expressed as SDS of general population standards (Prader et al., 1989), were evaluated in 130 TS pts with TS at the 1st observation (10.30±3.19 yrs) and at FH, reached after 6.9±2.9 yrs of GH-therapy. Thirteen subjects had Y-mosaicism (9%), 38.2% X-monosomy, 36.1%, X-structural abnormalities and 16.7% X-mosaicism. 27 pts of Y-negative group experienced spontaneous menarche (18.7%). 100 pts were treated with GH therapy for >4yrs and 81 pts for >8yrs. At baseline no differences were found between Y-positive and negative subjects, also in Target Height.
Results: The patients treated >6yrs showed a significantly higher increase in FH than < 6yrs patients, while the increase in sitting height was lower, obtaining a better result in body proportions. FH appeared significantly influenced by GH-therapy duration, negatively by menarche, but not by Y-chromosome material. In fact, FH was not different in Y-positive and Y-negative group. SDS-increases in subischial leg length (SLL) (2.2 vs 1.1 SD) was significantly

higher (p=0.01) in in Y-positive group.
Conclusions: GH therapy at high doses and long duration improved FH and body proportions in both the groups of TS pts, with or without Y-chromosome mosaicism. No differences were found in FH, while the increase in SLL-SDS was significantly higher in Y-positive pts compared with Y-negative. In our study Y-positive subjects treated with long term GH-therapy seem to obtain better body proportions.

P1-d1-572 Sex Differentiation 1

Characteristic testicular histology is useful for the identification of *NR5A1* gene mutations in prepuberty 46,XY patients

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Background: Individuals with *NR5A1* mutations encoding Steroidogenic factor-1 (SF1) develop a phenotypically broad range of disorders of sexual development (DSD). Based on literature review, we noted that hypoplastic seminiferous tubules and the emergence of Leydig cells with vacuolar cytoplasms are seen predominantly in the majority of individuals with *NR5A1* mutations. It has not been fully established whether these features are pathognomonic.
Aim: The aim of this study was to address if the histopathological characteristics of the testis can be a biomarker for 46,XY individuals with *NR5A1* mutations.
Design: In order to ascertain whether or not the histological features were the characteristics of *NR5A1* mutations, we screened the testicular histology of 242 patients under 10 years old with a 46,XY DSD who underwent gonadectomy or biopsy. These 242 patients were composed of 222 with unilateral or bilateral undescended testes, 5 with hypospadias with undescended testes, and 15 with ambiguous genitalia or complete female. We subsequently assessed *NR5A1* mutations.
Results: Of 242 patients with 46,XY DSD, six patients matched histological testicular features: a reduced number of thin seminiferous tubules and focal aggregations of Leydig cells that contained cytoplasmic lipid droplets. All six patients had novel *NR5A1* mutations. These histological features were distinct from those of other DSD.
Conclusions: We propose that testicular histology is a useful marker for the identification of *NR5A1* mutations in 46, XY patients with DSD before puberty.

P1-d1-573 Sex Differentiation 1

Lims1: a new androgen receptor coregulator expressed during male genital development

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Background: The embryonic development of male external genitalia is strictly dependent on androgens during a short critical time window. Androgen action is mediated by the androgen receptor, a nuclear receptor that functions as a transcription factor in a concerted action with coregulators.
Objective: To identify coregulators, that support AR action during external genital development in the male embryo.
Method: We performed yeast two-hybrid screenings with three independent cDNA libraries of genital tubercles from male mouse embryos of embryonic days E15, E16 and E17 using the DNA- and ligand-binding domain of human AR as a bait.
Results: Lims1 was identified in 6 independent clones in all three libraries. Retransformation of yeast with shortened AR-baits revealed that AR-Lims1 interaction is DHT dependent and the ligand binding domain of the AR is sufficient to mediate this interaction. The interaction was confirmed in vitro by GST-pull down assays and in vivo by coimmunoprecipitation experiments. LIMS1 caused an enhancement of AR transcriptional activity at two different promoters in Cos1 cells. Mutation of the FQMLF motif in LIMS1 to FQMAA reduced its coactivator function. In LNCaP cells RNAi-mediated knockdown of LIMS1 leads to up-regulation of the endogenous androgen-regulated genes TMPRSS2 and PSA.
Conclusion: Depending on the cell type, LIMS1 may act as a coactivator or corepressor of androgen receptor dependent transcription.

P1-d1-574 Sex Differentiation 1

Satisfaction with hormone replacement therapy (HRT) and vaginal function in orchiectomised women with complete androgen insensitivity syndrome (CAIS)

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Background: Standard of care for CAIS includes routine orchiectomy and postpubertal HRT. However, little information regarding perceived physical and emotional changes following orchiectomy is available. Similarly, data regarding satisfaction with HRT and sexual function are limited.
Objective: To characterize history, clinical management and self-reported satisfaction with HRT and vaginal function in a cohort of CAIS women post-orchiectomy.
Methods: Questionnaires regarding demographics, treatment history, HRT and vaginal function were completed at home by 30 women with CAIS ascertained via a support group.
Results: Median (range) age was 49.4 (23.6-76.4) yr; 19 (63%) were married or cohabiting, 17 with men. Response to the question "Do you consider yourself intersexed?" was "yes" for 50%. Most women (77%) were diagnosed during teen or adult yrs, 60% due to amenorrhea. Orchiectomy was performed during childhood or early teens in 43%; after puberty in 57%. Changes reported after postpubertal orchiectomy included reduced libido, 47%; weight gain, 41%; withdrawal, moodiness or depression, 35%. All women had received HRT, consisting of estrogen alone in 24 (80%), and in combination with testosterone in 4. Satisfaction with HRT (5-point Likert scale) was high: 71% scored this ≥4. In contrast, 79% reported incomplete satisfaction with vaginal function; 73% rated vaginal size as "smaller than average" or "very small"; 2 women who underwent skin graft vaginoplasty at ages 28 & 36 yr rated satisfaction as 3. Most common reasons for dissatisfaction with vaginal function were difficult or painful intercourse, 56%; inadequate lubrication, 33%.
Conclusions: In this cohort of predominantly heterosexual women with CAIS almost half reported reduced libido following orchiectomy and 41% reported weight gain. Although satisfaction with standard HRT was high, most women reported incomplete satisfaction with vaginal function. Management for AIS needs to be optimized for long-term outcomes.

P1-d1-575 Sex Differentiation 1

Duplication of the SOX3 gene in a SRY negative 46,XX male hypoplasia of the right kidney and hypospadias

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Introduction: An 11 old patient with hypoplasia of the right kidney and hypospadias was found to be SRY negative, 46, XX. His parents and younger sister were healthy. His intelligence was normal (IQ 92) and he had no other anomalies. The behavior, growth and development were all normal. His testes were >4ml and the penis was 5 cm.

Case study: Ultrasound and MRI did not show internal female genitals, while confirming right kidney hypoplasia (as did the DMSA scan).
ACTH test showed normal basal and stimulated 17OH-progesterone excluding a form of 46XX DSD due to 21-hydroxylase deficiency. 11-DOC and 11S were normal at both baseline and after ACTH stimulation, excluding 11BHSD deficiency. Cortisol levels were in the mid normal range at baseline and responded to stimulation, excluding primary adrenal insufficiency. Androstenedi-one, DHT and testosterone were in the middle to upper normal range for age and male sex.
The hCG test found testosterone in the low normal range for male sex and age at baseline. It rised up to 146 ng/mL indicating the presence of functional Leydig cells targeting by the hCG. The stimulated ratio T:DHT was 5.6, not supporting 5 alpha-reductase deficiency.
SNP array for copy number variations (CNV's) showed a unique 550 kb duplication involving SOX3, RP1-177G6, and CDR1 genes, and the microRNA MIR320D2. This CNV was absent in 13,839 controls.
Conclusions: A SRY negative 46,XX male with renal hypodysplasia was found to have an exceedingly rare duplication involving the SOX-3 gene, suggesting a role in both sex determination and kidney development.

P1-d1-576 Sex Differentiation 1

Abstract has been withdrawn

P1-d2-577 Sex Differentiation 2

Molecular analysis of 5-alpha-reductase type 2 gene in patients with 46,XY DSD

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Background: The conversion of testosterone in dihydrotestosterone mediated by 5alpha-reductase type 2 enzyme (*SRD5A2*) is an essential process for the normal sexual differentiation of male external genitalia. Mutations in *SRD5A2* gene result in 46,XY disorder of sex development caused by null or decreased synthesis of dihydrotestosterone. Affected individuals may present either ambiguous genitalia or normal female phenotype.
Objective: The purpose of this research was to screen for *SRD5A2* nucleotide variations in 90 patients with clinical and hormonal characteristics 46,XY DSD without androgen receptor gene mutations.
Method: The five exons of *SRD5A2* gene including exon-intron junctions were sequenced.
Results: A total of 9 single nucleotide variations (SNVs) were identified in 12 non-related individuals (13%). Four novel SNVs located in an intron or at a splicing region were identified: c.544G>A, in the splicing site in exon 3; c.278delG, in the donor splicing site within exon 1; and c.442+86A>G, c.545-44T>G and c.545-32A>T, located in intron 2 and 3. Three previously described mutations have been also identified in those patients: c.418delT, p.Gln126Arg and p.Gly196Ser. Five individuals, including two siblings, were homozygous for p.Gln126Arg and 2 were compound heterozygous for p.Gln126Arg and p.Gly196Ser (n=2). Two individuals were homozygous for c.544G>A mutation, and one presented compound heterozygosis for c.544G>A and c.418delT. Finally, one patient was homozygous for c.418delT, one compound heterozygous c.418delT and p.Gly196Ser.
Conclusions: The most frequent mutation in this cohort was p.Gln126Arg, which represented 50% of the affected alleles. Such data probably reflect a founder effect for this mutation in Southern East Brazil. *In silico* studies for novel SNVs demonstrated that they might create or abolish protein recognition sites involved in normal splicing mechanism. Additional *in vitro* studies are necessary to demonstrate such interference in mRNA process.

P1-d2-578 Sex Differentiation 2

Molecular analyses using next-generation technologies for 141 patients with disorders of sex development

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Background: Recently, novel techniques including next-generation sequencing (NGS) and array-based comparative genomic hybridization (CGH) have been developed for molecular analysis of human DNA samples.
Objective and hypotheses: We aimed to clarify the molecular bases of disorders of sex development (DSD) using NGS and CGH.
Methods: The present study consisted of two patient groups. Group 1 (n=46): Patients with 46,XY and 46,XX DSD who manifested severe genital abnormalities. This group was subjected to target-enrichment analysis for 35 disease-causative and 85 candidate genes for DSD. Furthermore, CGH analysis was carried out for patients with 46XY DSD. Group 2 (n=95): Patients with 46,XY DSD who showed mild genital abnormalities (hypospadias and/or cryptorchidism). This group was subjected to amplicon-sequence analyses for 10 causative and 10 candidate genes.
Results:
Group 1: NGS identified 69 nucleotide substitutions in 31 patients. Of the 31 patients, 11 had mutations in known disease-causative genes such as AR, SF1 and SOX9, whereas 32 had nucleotide substitutions in candidate genes. CGH identified cryptic copy-number abnormalities in 3 patients: deletions at 9p24.1-24.3 involving *DMRT1*, at 2q31.1-32 involving *HOXD* genes, and at 20p13 affecting a genomic interval that has not been implicated in male sex development.
Group 2: NGS identified 16 nucleotide substitutions including 1 mutation in a causative gene and 4 mutations in candidate genes.
Conclusion: The present study indicates that NGS and CGH serve as powerful tools for mutation screening of DSD. These methods are useful for molecular diagnosis of DSD and for identification of novel molecular abnormalities possibly associated with DSD. Further *in vitro* and *in vivo* studies for the candidate mutations and deletions identified in this study will clarify novel mechanisms leading to DSD.

P1-d2-579 Sex Differentiation 2

Effect of exposure to bisphenol A on hippocampal cell proliferation: a sexual dimorphism

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Background: Bisphenol A (BPA) is a ubiquitous endocrine disrupting chemical (EDC) causing deleterious effects through alteration of thyroid and sex steroid functions especially in developing organisms. Recently it has been

shown that perinatal exposure to EDC affects hippocampal neuronal plasticity, thereby potentially modulating neuronal development and leading to impaired cognitive functions.
Objective and hypotheses: We hypothesize that BPA-induced hippocampal neuronal plasticity might be age- and sex-related.
Methods: Pregnant and lactating C57/BL6 mice were treated orally with 50 µg/kg/day of BPA or corn oil from the first day of gestation until weaning at postnatal day 21 (P21). Hundred µm-sections of the dorsal hippocampus of male and female pups at P7, P14, and P21 were immunostained for Ki67 in order to label proliferating progenitors. Confocal Z-stack images of the dentate gyrus were analyzed to quantify the number of newborn neurons in the subgranular zone. Data are expressed as mean±SD (n=5 males and 5 females per group).
Results: The number of proliferating progenitors in the subgranular zone of the dentate gyrus was sexually dimorphic since the average number of Ki67+cells per section was higher in female controls compared to male controls at P14 (81±5 vs 70±6; $p< 0.01$). The average number of proliferating cells per section was not affected by BPA treatment in males at P7 (78±1 vs 78±3), P14 (61±10 vs 70±6) and P21 (47±7 vs 50±5) when compared to controls. However, age-related decreased progenitor proliferation seems more affected by BPA treatment in males. Interestingly, BPA increased the number of Ki67+cells in females at P14 (99±11 vs 81±5; $p< 0.01$).
Conclusions: Our data suggest that perinatal exposure to BPA increases progenitor proliferation in the dentate gyrus preferentially in immature females. This effect is not observed in immature males. The underlying mechanism of perinatal BPA effect on female hippocampus still needs to be unraveled.

P1-d2-580 Sex Differentiation 2

Pubertal course of 45,X/46,XY MGD patients raised as girls

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Background: Gender assignment is a difficult question in 45,X/46,XY neonates with ambiguous genitalia, partly due to the paucity of large clinical studies. We have previously reported that 45,X/46,XY patients raised as boys have short stature, altered pubertal course, testicular failure and impaired fertility.
Objective, methods and population: We describe the pubertal and long term outcome of thirty-one 45,X/46,XY mixed gonadal dysgenetic (MGD) patients raised as females in a retrospective French multicentric study.
Results: Mean age was 26±1.6 years (16-55). At birth, 62% presented with asymmetrical external genitalia, 100% with perineoscrotal hypospadias. Mean genital tubercle was 20±1.6 mm length. This phenotype was associated with a hemi-uterus on the streak gonad side and a contralateral dysgenetic testis in most cases. 48% of the patients were born with an *in utero* growth retardation and 71% developed features of Turner syndrome. All patients had bilateral gonadectomy during the first surgery at a mean age of 13.5±2.6 months. Puberty was hormonally induced in all girls at a mean age of 13.8±0.4 years, using either ethinyl-estradiol or 17beta-estradiol. The mean pubertal growth spurt was 11.8±0.9 cm, with a final height of 153.9±1.1 cm (BMI 24±0.9 kg/m^2), regardless of growth hormone treatment. Most girls (78%) reached a 4-5 Tanner stage of breast development. Uterus length reached a 60-80 mm range in 40% of the patients and vaginal size was normal (7-13 cm) in 88%. As adults, half of the patients were satisfied by their physical appearance, 60% had an active sexual life with 23% experiencing satisfying intercourses.
Conclusions: This first large cohort study of 45,X/46,XY MGD patients raised as girls, demonstrates suitable final stature and pubertal development, although improvable long-term outcomes, that should be taken into consideration for gender assignment.

P1-d2-581 Sex Differentiation 2

Characterization of a novel CYP19A1 (aromatase) R192H mutation with severe virilization of the 46,XX newborn but without virilization of the mother during pregnancy

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Background: P450 aromatase (CYP19A1) is essential for estrogen biosynthesis from androgen precursors. Mutations in the coding region of CYP19A1 lead to aromatase deficiency. To date over 20 subjects have been reported with aromatase deficiency which may manifest during fetal life with maternal virilization and virilization of the external genitalia of a female fetus due to low aromatase activity in the steroid metabolizing fetal-placental unit. During infancy, girls often have ovarian cysts and fail later to enter puberty showing signs of variable degree of androgen excess. Moreover, impact on growth, skeletal maturation and other metabolic parameters is seen in both sexes.
Objective and hypotheses: We found a novel homozygote CYP19A1 mutation in a 46,XX girl who was born at term to consanguineous parents. Although the mother did not virilize during pregnancy, the baby had a complex genital anomaly at birth (enlarged genital tubercle, fusion of labioscrotal folds) with elevated androgens at birth, dropping thereafter. Presence of 46,XX karyotype and female internal genital organs (uterus, vagina) together with biochemical findings and follow-up showing regression of clitoral hypertrophy, elevated FSH with ovarian cysts suggested aromatase deficiency. To confirm the clinical diagnosis, genetic and functional studies were performed.
Methods and results: Genetic analysis revealed a homozygote R192H mutation in the CYP19A1 gene. This novel mutation was characterized for its enzymatic activity (Km, Vmax) in a cell model and found to have markedly reduced catalytic activity when compared to wild-type aromatase; thus explaining the phenotype. Protein model studies suggest that R192H disrupts substrate binding and may exert variable effect on different substrates.
Conclusions: R192H is a novel CYP19A1 mutation which causes a severe phenotype of aromatase deficiency with regressive virilization of the 46,XX newborn, but without signs of androgen excess during pregnancy.

P1-d2-582 Sex Differentiation 2

Molecular studies in four patients with SRY-positive 46,XX disorders of sex development: implications for the development of normal and abnormal male external genitalia

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Background: SRY-positive 46,XX disorder of sex development (DSD) is occasionally accompanied by ambiguous external genitalia. Although this phenomenon may be explained by spreading of X-inactivation into SRY or disruption of SRY expression by position effect, the precise mechanism(s) remains to be clarified. Here, we attempted to clarify this matter.
Patients and methods: This study consisted of three patients with 46,XX

DSD and normal external genitalia (cases 1-3) and one patient with 46,XX DSD and ambiguous external genitalia (case 4). We examined the sizes of translocated Y chromosomal materials, those of deleted X chromosomal materials, the translocation fusion points, the X-inactivation patterns, and the SRY sequences.
Results: The sizes of trans located Y chromosomal material were 2.7-9.1 Mb in cases 1-3 and 3.4 Mb in case 4, with the breakpoints proximal to SRY. The sizes of deleted X chromosomal materials were 1.8-3.6 Mb in cases 1-3 and 6.4 Mb in case 4, with the breakpoints residing on the pseudoautosomal region (PAR1) in cases 2 and 3 and on the X-differential region in cases 1 and 4. Furthermore, the translocation in case 1 was mediated by a homologous sequence (PRKX and PRKY) with an inversion involving PRKY. Cases 1-4 had random X-inactivation and normal SRY sequence.
Conclusions: Although there was no obvious difference in the size of the translocated Y chromosomal material and the X-inactivation pattern between cases 1-3 and case 4, the size of X chromosomal deletion was larger in case 4 than in cases 1-3. Furthermore, the X-chromosomal breakpoint of case 4 resided on the X-differential region subject to X-inactivation, whereas the breakpoints of cases 1-3 lied on the PAR1 or PRKX escaping X-inactivation. Thus, it might be possible that the spreading of X-inactivation into SRY occurred in case 4, leading to ambiguous external genitalia.

P1-d2-583 Sex Differentiation 2

Analysis of *Sox9* gene expression regulatory region in 46,XY DSD patients without campomelic dysplasia

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Background: Among several genes other than *SRY*, *SOX9* (*Sex Determining Region Y-box 9*) is considered essential to drive the male pathway in the undifferentiated gonad. Inactivating mutations in *SOX9* coding region cause the skeletal disorder campomelic dysplasia associated with 46, XY sex reversal. Upstream SOX9 gene there is a gonad-specific enhancer that mediates testis *SOX9* expression called "TESCO". Indeed, Sry along with Sf1 binds to multiple elements within the TESCO. Thus, mutations in this region should determinate decreased SOX9 expression leading to abnormalities of testicular development.
Objective: To analyze the TESCO in 46,XY DSD patients due to disorders of gonadal development (46, XY DGD) without campomelic dysplasia or in those with indeterminate cause.
Patients and methods: We studied 37 patients with 46, XY DGD and 38 with undetermined 46, XY DSD. Mutations in several genes involved in gonadal development including *SOX9* coding region, was previously ruled out in 46,XY DGD patients and defects of testosterone synthesis, 5 alfa-reductase 2 deficiency and partial androgen insensitivity were excluded in the patients with undetermined 46,XY DSD. The entire TESCO region was amplified and sequenced from genomic DNA.
Results: We identified a heterozygous allelic variant at genomic position g. 70104091C>A within TESCO region (Genomic browser Ensembl). This variant was found in 8 patients and was previously described as a polymorphism, since it has been found in 29,2% of the world population.
Conclusion: No mutation or new allelic variants were found within TESCO in a large cohort of 46,XY DSD patients indicating that the testis *SOX9* expression regulatory region as well as *SOX9* coding region are rarely involved in the aetiology of 46,XY DSD without campomelic dysplasia.

P1-d2-584 Sex Differentiation 2

Achieving clarity in the molecular pathogenesis of 46,XY DSD

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Background: Disorders of Sex Development (DSD) in 46,XY cases primarily comprise defects in testis development, in androgen production or androgen action as causation. Clinical and biochemical phenotyping underscore generic diagnosis but specificity relies on analysis of the relevant candidate genes.
Objective and hypotheses: To analyse a large DSD database by determining the validity of sequencing five candidate genes for a specific diagnosis in XY DSD and identify novel mutations.
Methods: A total of 348 cases were selected based on adequate data to suggest a clinical diagnosis verifiable by analysis of; *SRY, NR5A1, HSD17B3, SRD5A2, AR.*
Results: The commonest cause of XY DSD was androgen insensitivity (AIS,75%) comprising 202 and 59 cases of CAIS and PAIS, respectively, proven by identifying mutations distributed across the *AR* gene. Of these, 25 were novel identified and are now the subject of model-based structural analysis. Defects in androgen production proven by identifying mutations in *HSD17B3* (n=31) and *SRD5A2* (n=40) comprised 20% of the total cohort. A third were compound heterozygous. Only 5% of this large study group had mutations in either *SRY* (n=9) or *NR5A1*(n=7), highlighting the continuing void in knowledge on genetic causes of defects in testis determination.
Conclusions: A large, well characterised phenotypic DSD database provides a suitable framework in which to assess whether clarity can be achieved to determine the molecular pathogenesis in the complex XY sub-group of DSD. This study confirms this is possible by not resorting to a cult shotgun sequencing approach, but combining thoughtful clinical investigation with targetted gene sequencing. The dataset has also revealed a significant number of novel mutations whose further study enables the physiology of androgen function to be better understood.

P1-d2-585 Sex Differentiation 2

Sexual dimorphism of *in vivo* rodent brain chemistry using magnetic resonance spectroscopy

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Background: By providing a non-invasive, functional insight, Magnetic Resonance Spectroscopy (MRS) has the potential to provide objective longitudinal data on mammalian brain development. Sexually dimorphic spectroscopy has been reported in humans but not in the rodent model.
Objective: To assess the sexual dimorphism in rodent brain chemistry using *in vivo* MRS.
Methods: Male and female Sprague Dawley rats (n=32, 16) were treated on postnatal days 1-5 with 50mg/kg flutamide SC or corn oil and scanned at 6wks and 10wks of age using a 7TMRI scanner. Spectra were obtained from a voxel in the frontal cortex. Metabolites were expressed as a ratio to creatine+phosphocreatine and the Mann Whitney test used for statistical analysis. Full width at half maximum (FWHM) was used as a marker of reliability.
Results: FWHM was within optimal range (12-18Hz). Anogenital distance(AGD) was reduced in treated males at 6wks and 10wks(MT6, MT10) when compared with control males(p=0.003, p=0.0185) and this remained significant when corrected for weight(p=0.0011, p=0.0235). Phallus length was reduced in MT6 and MT10(p=0.02, p=0.0008) and phallus weight reduced in MT10(p=0.0009). In control males, there was a decrease from 6wks to 10wks in 3 metabolite ratios: GABA(p=0.042), glutamine(p=0.031) and glutamate(p=0.022). In control females there was also a decrease in glutamine and glutamate from 6wks to 10wks(p=0.0277, p=0.0236). Myo-inositol was higher in treated males compared to control males(p=0.0003, p=0.017) and levels trended towards those in the female controls(ns).
Conclusions: Effects of neonatal androgen blockade are manifested in the male rat as undermasculinisation of the genitalia as well as a brain metabolite pattern which resembles that in the female rat. Age related changes were also demonstrated. MRS is a reliable tool for studying the brain in maturing rats and may be a useful tool for studying the link between longitudinal changes in sex steroids and brain metabolism.

P1-d2-586 Sex Differentiation 2

Progestogen exposure in the male programming window reduces birth weight and affects sex development of offspring

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Background: Progestogen exposure in both humans and mice can lead to foetal genital anomalies including hypospadias, but a detailed study of their effects during the male programming window on parameters such as the anogenital distance (AGD) has not been performed.
Objective and hypotheses: To investigate the effect on AGD of medroxyprogesterone acetate (MPA) given in the male programming window.
Methods: Pregnant Sprague Dawley rats were treated with either 75mg/kg or 150mg/kg of MPA (MPA75, MPA150), or vehicle alone (Control) subcutaneously once daily from e14-17. All pups were culled on day1, weighed and AGD measured. Animals were sexed by internal anatomical structures and testes were dissected and weighed. All data are presented as mean±1SD.
Results: The birth weight in Control (n,24), MPA75 (n,15) and MPA150 (n,12) groups were 6.12g(0.71), 4.91g(0.44) and 4.58g(0.24), respectively ($p< 0.001$). Birth weight did not differ by sex in any group. MPA did not affect litter size.
In the male MPA75 (n,9) and MPA150 (n,6) groups, mean AGD was 2.63mm(0.56) and 2.60mm(0.51), respectively; lower than control male AGD (3.41±0.33; n,7) ($p< 0.001$). In the female MPA75 (n,6) and MPA150 (n,6) groups, mean AGD was 2.33mm(0.46) and 2.90mm(0.27), respectively; greater than control female AGD (1.7±0.21; n, 17) ($p< 0.001$). Whilst male control AGD was greater than control female AGD ($p< 0.001$), there was no AGD sex difference after MPA exposure.
Testis weight in the MPA75 and MPA150 groups was 0.0037g(0.0012) and 0.0031g(0.0013) respectively, and showed a small but not significant decrease from Controls at 0.0051g(0.0023) ($p=0.11$).
Conclusions: MPA exposure of rats in-utero is associated with a lower male AGD but higher female AGD. Both sexes show marked intra-uterine growth restriction in response to MPA exposure. The mechanisms of this require further investigation along with the possible effects of prenatal progestogen exposure in human models.

P1-d2-587 Sex Differentiation 2

Decreased expression of four memory genes in non-syndromic cryptorchid males

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Background: Egr1 has been widely recognized as essential for some aspects of learning and memory while Egr 4 has been shown to be involved in receptor - modulated memory processes. Furthermore, it has been shown that testosterone enhances memory by increasing biological salience of incoming information. In cryptorchid boys, an elevated odd ratio for low IQ was found. (1) It is postulated that the hypothalamus-pituitary-testicular axis is implicated in maintaining the similarity of gene expression between brain and the testis.
Objective and hypothesis: We hypothesize that infertile cryptorchid males may have impaired expression of several memory genes in their testes.
Patients and methods: Whole genome analysis of testicular biopsies from 7 boys who underwent orchiopexy with typical testicular histology of a high risk infertility group (HIR) were compared to 12 biopsies of cryptorchid boys with low risk for developing infertility (LIR) utilizing Affymetrix microarrays and quantitative real time PCR and immunohistology.
Results: The HIR group had low or lack of expression of the following memory genes compared to LIR: EGR1, EGR4, FMR2 and VCX3A. [Median values, log2; EGR4 2.7 vs. 5.65 $p< 0.0006$, EGR1 7.49 vs. 9.2 $p< 0.027$ FMR2 4.71 vs. 6.03 $p< 0.003$, VCX3A 5.9 vs. 7.46 $p< 0.01$] Immunohistologic analysis revealed lower EGR1/EGR4 expression in the spermatogonia of the HIR group as compared to LIR testes.
Conclusion: Impaired expression of four memory genes known to encode for proteins involved in signalling pathways regulating cytoskeleton organization, synaptic vesicle transport and establishment of connections between neuronal cells may contribute to reduced intellectual and cognitive functions of cryptorchid males. The current findings provide new insight into potential molecular mechanisms into crucial processes for the development of these functions.

P1-d2-588 Sex Differentiation 2

A novel heterozigous mutation in steroidogenic factor 1 in a 46,XY patient with ambiguous genitalia but without adrenal insufficiency

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Background: Steroidogenic Factor 1 **(**SF1) (NR5A1) is a nuclear receptor that regulates the expression of genes involved in gonadal and adrenal development, steroidogenesis and the reproductive axis. We report the case of a newborn with 46,XY DSD and normal adrenal function due to a novel heterozygous NR5A1 mutation, assigned to female sex at birth.
Case report: An 8 months-old female child was referred to our Unit because of clitoromegaly. She presented with microphallus (length 2.7 cm; thickness 0.8 cm), fusion of the labioscrotal folds, and palpable inguinal gonads. Neither uterus or other mullerian structures were found. Hormonal assessment revealed normal adrenal function, AMH and Inhibin B with low normal values of serum testosterone. Karyotype was 46,XY. No mutations in both 5-alpha reductase and androgen receptor (AR) genes were found. ACTH stimulation test revealed normal cortisol synthesis. Standard and prolonged HCG stimulation test showed an impaired androgens response. Normal gonadotropin peak after an LHRH stimulation test ruled out a resistance to LH. Molecular analysis of the NR5A1 gene showed heterozygous c.937C>T mutation in the exon 5. A four months trial with Testosterone enanthate (25 mg) resulted in a significant increase in phallic length (from 2.7 to 4 cm) and thickness (from 0.8 to 2 cm). Therefore, according to parental wishes, gender reassignment to male was enstablished.
Conclusions: The spectrum of phenotypes associated to SF-1 mutations may be wide, ranging from gonadal agenesis to milder forms of partial testicular dysgenesis, with or without adrenal insufficiency. Clinical and hormonal features in patients with SF-1 mutations may mimic a partial androgen insensitivity or a resistance to LH, making the diagnosis and correct gender assignment challenging. Our case suggests that screening for SF-1 mutations should be performed in subjects with 46,XY DSD with no mutations in the AR gene even in absence of adrenal insufficiency.

P1-d1-589 Thyroid 1

Clinical usefulness of sonoelastography in differential diagnosis of thyroid nodules in children and in young adults

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Background: Sonolelastography is a new imaging technique that allows to establish the vibrational response of soft tissue to forced harmonic oscillation during casual US examination. This property can be used in differentiating diagnosis of thyroid lesions.
Objective and hypotheses: The aim of this study was to establish the usefulness of sonoelastography in the assessment of thyroid nodules in children and young adults.
Methods: The study included 80 patients with 97 thyroid nodules.. All patients were examined using Toshiba UIMV-A500A Hitachi sonolelastography, ASQ (Acoustic Structure Quantification) and MicroPure (microcalcifications detection). The elastic parameters of strain ratio (SR, SR1 was calculated using the same-level and normal-appearing thyroid region as reference) were assessed. The sensitivity, specificity were analyzed. The results were compared with postoperative cytology and histology results.
Results: Results were interpreted based on following criteria: elastography strain scale; types of nodules vascularisation; size of the nodules in relation to their topography; present or not hipoechogenic halo in tissues around the

nodules.Histology revealed 95 benign lesions and 4 malignant lesions. SR1 and SR were different for benign and malignant tumor. In benign nodules SR and SR1 exhibited moderate diagnostic performance - area under the curve 0,78 -1,84. In 4 malignant tumors elasticity parameters were different. Patients with malignant tumors presented type II/III, IV and B2, C of type of vascularisaction. The presence or the absence of the ring sign of slightly stiffer tissue around the lesion were detected in ASQ procedure.The increase in sensitivity was statistically significant.
Conclusions: The elasticity values of benign and malignant lesions were significantly different allowing for accurate characterization. Additional use of sonoelastography increases the diagnostic accuracy of B-mode US.

P1-d1-590 Thyroid 1

The improvement of mental development by early L-thyroxine therapy of secondary hypothyroidism in preterm-born children with low body weight

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Background: Secondary hypothyroidism is observed in children after brain damage. Especially in preterm-born and in children with low, and very low body weight. This disorders is not detected by screening because low levels of TSH.
Objective and hypotheses: The aim of the study is evaluation of mental development in preterm-born children during replacement therapy with l-thyroxin because the secondary hypothyroidism. The motor and mental development 42 preterm new-borns with secondary hypothyroidism treated with l-thyroxin since the second week of life were compared with the development of 52 preterm new-born with secondary hypothyroidism treated since the fourth week or later.
Methods: The motor development was evaluated, and the mental development and IQ was assessed in the Wechsler Intelligence Scale for Children in the seventh year of life.
Results: Earlier achievement of the milestones of motor development i.e. sitting, standing, and walking was observed in children from group who received early treatment with modest doses of l-thyroxin. In this group, all infants acquired the motor functions statistically significantly earlier in comparison to the infants from group with delayed treatment. In the seventh year of life, the IQs were significantly higher in group I treated since the second week of life in comparison to group II.

	I Group IQ	II Group IQ	p
Total	102.6±20.1	82.3±21.3	0.003
LBW	107.2±22.7	89.1±23.5	0.002
VLBW	99.3±23.7	83.3±13.4	0.007
EVLBW	99.0±11.8	62.0±19.0	0.001

[IQ in preterm new-born]

Conclusions: The early replacement therapy with l- thyroxin initiated in the second week of life may improve long-term mental development in preterm-born children.

P1-d1-591 Thyroid 1

Maternal hypothyroxinaemia in pregnancy and impact on the mental development of their children

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Background: It has been considered that maternal hypothyroxinemia (MH) in the first trimester of pregnancy can affect mental development in the offspring, even with normal TSH levels. TPO autoantibodies (TPO-Ab) detected in the pregnancy has been denoted as a poor predictor for neurological development.
Objectives and hypotheses: To assess whether or not there is a relationship between the FT4 levels or the presence of TPO-Ab in pregnant women, with their children's intelligence quotient (IQ). To evaluate if the presence of MH determines a low IQ in the offspring.
Methods: Thyroid function (FT4 and TSH), TPO-Ab and iodine urinary excretion were analyzed in 2246 pregnant women, in the first (1T) and second (2T) trimester of pregnancy. We determined the 10th percentile for FT4 (1.1 ng / dl in 1T and 0.93 in 2T). In 310 children, IQ (WISC-IV) was assessed at 6-8 years of age and compared with a control group (51 children whose mothers remained normal urinary iodine excretion, FT4> p10 and negative TPO-Ab in both trimesters).
Results: No relation was found between the presence of MH and IQ in the offspring. The mean IQ in children born from mothers with FT4 < p10 in 1T or 2T were not different from the rest population or the control group. Children from mothers with low urinary iodine excretion in 1T did not have a lower IQ. Considering children with IQ extremes [IQ> 110 (n=122) or IQ < 90 (n=32)] there were not differences in relation with maternal FT4. Children born form women with positive TPO-Ab (n = 44) did not have a low IQ.
Conclusions: In this study we did not find a relationship between MH and their children's IQ.
Those children born from mothers with FT4 < p10 did not show lower scores on the test.
No relation was found between positive TPO-Ab in pregnancy and their children's IQ.

P1-d1-592 Thyroid 1

Clinical and biochemical risk factors in children with untreated long-term idiopathic subclinical hypothyroidism

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Background: Subclinical hypothyroidism (SH) is a biochemical condition characterized by increased serum levels of TSH with normal values of FT4. In adults SH has been associated with high low-density lipoprotein-cholesterol (LDL-C) and homocysteine (Hcy) levels and increased risk of atherosclerosis, while data in untreated SH children are scanty.
Objective: To investigate clinical and biochemical atherosclerotic risk factors in children with untreated idiopathic SH.
Methods: Fourty-nine children with long-term (3.1±0.4 years) idiopathic SH, aged 7.8±0.5 years, underwent height, weight, waist and hip circumference measurements. The degree of overall adiposity was expressed as BMI. Waist to hip ratio (WHR) and waist to height ratio (WHtR) were used as indicators of abdominal adiposity. Lipid profile, Hcy levels and atherogenic index (AI) were evaluated. Forty-nine healthy euthyroid children, matched for age and sex, were enrolled as controls.
Results: In SH children and in controls BMI and WHR were similar. WHtR was higher in SH subjects than in controls (0.52±0.01 vs 0.41±0.03,p < 0.01)

and was positively correlated to TSH levels at study entry (r=0.3, p< 0.05). TC and LDL-C levels were similar in the two groups, while HDL-C was lower in SH children compared with controls (53.1±2.0 vs 61.8±2.0 mg/dl, p< 0.04) and AI was higher (3.2±0.1 vs 2.7±0.1, p< 0.005). A trend toward higher triglycerides levels was observed in SH subjects compared to controls (69.2±4.7 vs 59.1±3.4, p< 0.09). Serum Hcy levels were significantly higher in SH subjects than in healthy children (8.7±0.3 vs 7.8±0.2, p< 0.02). Serum HDL-C and Hcy were correlated with the duration of SH (r=-0.32, p< 0.03; r=0.38, p < 0.007, respectively), while AI was correlated with mean TSH levels from time of SH diagnosis to study entry (r=0.37, p < 0.05).
Conclusions: Untreated SH in children is associated with increased abdominal adiposity, pro-atherogenic abnormalities of lipid profile and increased Hcy levels.

P1-d1-593 Thyroid 1

Two novel mutations in the *TITF1/NKX2.1* gene in two Japanese families with Brain-Thyroid-Lung syndrome

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Background: *TITF1/NKX2.1* mutations cause Brain-Lung-Thyroid syndrome (BTLS), characterized by congenital hypothyroidism, benign hereditary chorea, and infant respiratory distress syndrome.
Objective: The aim of this study was to perform functional studies on two novel *TITF1* mutations and clarify the molecular mechanisms of its pathogenesis.
Methods: We analyzed all coding exons and flanking introns of *TITF1* gene in two Japanese families with clinical features of BTLS by PCR and direct sequencing. To generate TITF1 expression vectors, TITF1 cDNA was cloned into pCMV-myc and pEGFPN1 vectors. Site-directed mutagenesis were conventionally done. The luciferase reporter vectors were constructed by inserting the promoter sequences of the human thyroglobulin(Tg) into a pGL4 vector. A transactivation assay was performed using dual-luciferase reporter assay system on Hela cells. Western blotting was performed with a mouse anti-myc monoclonal antibody. For subcellular localization analyses, we visualized and photographed Hela cells transfected with GFP-tagged TITF1. For EMSA experiment, we used biotin-labeled doublestranded oligonucleotide.
Results: We identified two novel heterozygous mutations (c.533G>C, p.R178P and c.574G>T, p.E192X) in the affected patients. Both R178P and E192X TITF1 had markedly reduced transactivation. Interestingly, a dominant negative effect of the R178P mutant was demonstrated. Western blot analysis showed that the expression of R178P was comparable to that of the wild type, whereas E192X was not detected. The R178P mutant localized to the nucleus. WT TITF1 showed specific binding to the elements, which were competed by excess amount of cold competitors. The R178P mutant showed abrogated DNA-binding ability.
Conclusions: We describe the two novel mutations in the *TITF1* gene. The results show that haploinsufficiency may not be the only explanation for BTLS. The detailed mechanisms of TITF1 transcriptional regulation still remain to be elucidated.

P1-d1-594 Thyroid 1

Thyroid disorders in children and adolescents with Prader-Willi syndrome: data from 299 Italian patients

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Background: Variable findings regarding thyroid function in subjects with Prader-Willi syndrome (PWS) have been found in the literature. The reported prevalence of hypothyroidism (HT) ranged from 2 to 32% while central hypothyroidism is 19%.
Objective and hypotheses: The aim of our Italian multicenter investigation is to report the thyroid function in patients with PWS in order to identify the prevalence of thyroid pathology.
Methods: Thyroid function tests were carried out on 299 children and adolescents with genetically confirmed PWS (183 boys) included at a median age of 2.9 years (0.2-17.9) and BMI of 17.6 kg/m2 (10.4-67.8). Subjects were classified according to thyroid function as: euthyroidism (EuT), congenital hypothyroidism (C-HT), hypothyroidism (HT - high TSH and low FT4), central hypothyroidism (CE-HT - low/normal TSH and low FT4), and subclinical hypothyroidism (S-HT - high TSH and normal FT4).
Results: In our study population the prevalence of EuT was 89.3%. C-HT was found in 1.7%, while the prevalence of HT was 3.7%. Eight out of 11 cases with HT were affected by CE-HT.

Genetic/Thyroid Function	EuT	CH	SH	HT	CE-HT
Deletion	135	3	4	3	5
Uniparental Disomy	97	2	7	-	2
Methylation	31	-	4	-	-
Other	4	-	1	-	1
Total No. (%)	267 (89.3)	5 (1.7)	16 (5.3)	3 (1.0)	8 (2.7)

[Thyroid dysfunction according to genetic diagnosis]

Conclusions: Thyroid axis dysfunction seems to be a frequent feature (10.7%) in subjects with PWS compared to the general population. However, we found a lower prevalence of HT in our PWS subjects respect to other national database that included fewer patients. Pediatricians should be aware of this association so this possibility is considered while evaluating PWS patients.

P1-d1-595 Thyroid 1

Twin study emphasises the importance of foetal environment as a determinant of individual T4 setpoint

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Background: The intra-individual variation in plasma free thyroxine (T4) concentration is much smaller than the inter-individual variation, suggesting an individual free T4 setpoint. Although the precise determinants for this individual setpoint remain unknown, both genetic and environmental determinants may be involved. For instance, postnatal T4 concentrations seem to be related to the foetal and maternal thyroid hormone state.
The Dutch Twin Register contains data on more than 87000 twins. The Dutch neonatal congenital hypothyroidism (CH) screening is primarily T4 based and performed on the 4th or 5th day of life. To study the influence of the foetal environment on the postnatal T4 concentration, we analyzed CH screening results in a large sample of mono- and dizygotic twin pairs.
Objective: To find out whether the individual T4 setpoint is mainly determined by genetic factors or by the foetal environment.
Methods: Neonatal CH screening results of 585 mono- and dizygotic twin pairs were retrieved from the National Institute for Public Health and the Environment (RIVM). A total of 215 monozygotic (MZ), 202 dizygotic same-sex (DZ), and 168 dizygotic opposite-sex (DOS) twin pairs were analyzed in a classical twin study.
Results: The correlation of T4 concentrations was higher in the MZ twin pairs, with a slightly higher correlation in females (correlation factor MZ males 0,6494, MZ females 0,671). Correlation factors in DZ twin pairs were: DZ males 0,53, DZ females 0,4838, DOS 0,48. Overall genetic factors accounted for 30% of the variation in T4 results and the environment for 34%.
Conclusions: The higher T4 correlation in MZ twin pairs compared to DZ twin pairs suggests a genetic determinant. However, the unexpectedly high correlation in DZ twin pairs indicates a strong environmental determinant. Since we compared neonatal T4 screening results, this study emphasizes the importance of the foetal environment in T4 setpoint determination.

P1-d1-596 Thyroid 1

Relationship between Th17 cells and antithyroid antibodies in patients with autoimmune thyroid disease

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Background: Up till now, altered balance of Th1 and Th2 immune cells has been postulated to play an important role in the pathogenesis of autoimmune thyroid diseases (AITD). However, recent studies on thyroid diseases suggest a new role for Th17 (T helper 17) cells that have been classified as a new lineage, distinct from Th1, Th2 and Treg cells. Despite wide interest, the role of Th17 cells in the pathogenesis of inflammatory and autoimmune diseases is still being debated.
Objective and hypotheses: The aim of the study was to estimate the relationship between circulating CD4+CD161+CD196+ and CD4+IL-17+ Th17 cells and antithyroid antibodies in patients with Graves' disease (GD, n=22, mean age ± SEM 14.3 ± 4 years), Hashimoto's thyroiditis (HT, n=37, mean age ± SEM 15±2 yrs) and in healthy controls (C, n=25, mean age ± SEM 15.2 ± 2 yrs).
Method: Polychromatic flow cytometry and several fluorochrome-conjugated monoclonal antibodies were applied to delineate Th17 cells with either CD4+CD161+CD196+ or CD4+IL-17+ phenotype using apparatus FACSCalibur (BD Biosciences).
Results: In untreated HT children we observed an increased percentage of CD4+CD161+CD196+ (7.1 ± 3.5 vs. 3.7 ± 1.8; $p < 0.04$) and CD4+IL-17+ (3.7 ± 2.7 vs. 1.4±0.4; $p < 0.01$) Th17 lymphocytes in comparison to the healthy controls. In GD children we did not reveal such abnormalities in the population of these cells. In cases with HT, a positive correlation between the percentage of CD4+IL-17+ and CD4+CD161+CD196+ T cells and serum level of anti-TPO antibodies ($r=0.48$; $p < 0.025$; $r=0.65$; $p < 0.01$; respectively) was detected.
Conclusions: We conclude that the increased percentage of Th17 cells and their positive correlation with anti-TPO in children with HT can suggest their role in initiation and development of immune and inflammatory processes in this endocrinopathy.

P1-d1-597 Thyroid 1

Abstract has been withdrawn

P1-d1-598 Thyroid 1

Clinical re-evaluation of congenital hypothyroidism (CH) in preterm infants with eutopic thyroid

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Background: A high incidence of thyroid dysfunction in preterm infants is reported. At present there is little data on the re-evaluation and follow-up in preterm children affected by CH.
Objective: To determine the clinical evolution of CH with eutopic thyroid in preterm infants and assess their clinical features.
Population and/or methods: We retrospectively evaluated 21 preterm children with CH and eutopic thyroid. All patients were identified by the neonatal screening program and started L-Thyroxine treatment between 4 and 109 days of life. Patients at the age of 2 years underwent clinical re-evaluation including thyroid function testing and thyroid ultrasonography after L-Thyroxine therapy withdrawal.
Results: The first screening (3-5 days) identified 14% of patients (n=3), while the second screening (15-30 days) identified 86% of patients (n=18).
At re-evaluation, 5 patients (24%) had permanent CH (s-TSH persistently >10 mU/L) which required reintroduction of therapy, 5 patients (24%) had persistent hyperthyrotropinemia (HT) (s-TSH 5-10 mU/L) and 11 infants (52%) had transient CH (s-TSH < 5 mU/L).
All patients affected by permanent CH and HT showed a low s-TSH value at diagnosis (< 25mU/L), whereas patients affected by transient CH showed s-TSH >25mU/L in 6 out of 11 cases.
The main clinical features of patients affected by permanent CH were: 1 case of assisted reproduction, 2 twins, 2 SGA, 1 maternal thyroiditis, 2 patients with malformations. In the neonatal period 2 patients required CPAP, 1 patient showed several complications (respiratory distress, anemia, intraventricular hemorrhage, sepsis).
Conclusion: In premature infants it is important to consider neonatal factors that may affect thyroid function. The evolution of CH remains difficult to predict. Our data emphasize the importance of diagnostic re-evaluation. Althought the majority of patients did not require the reintroduction of therapy at re-evaluation, patients with HT required a close follow-up.

P1-d2-599 Thyroid 2

Expression of preproghrelin gene and ghrelin receptor family in thyroid tissues from paediatric patients with immune and non-immune thyroid diseases

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Background: The preproghrelin gene is responsible for generating ghrelin and obestatin, two gastric peptides with opposite effects on food intake. Obestatin suppresses food intake and digestive motility through interaction with GPR-39 (GPCR). Ghrelin is supposed to be a link connecting metabolism and energy homeostasis with growth as the result of activation of the growth hormone secretagogue receptor (GHSR).
Objective and hypotheses: The aim of the current study was to assess the expression of preproghrelin, GPR-39 and GHSR in thyroid tissues from patients with Graves' disease (GD, n=15), non-toxic nodular goiter (NTNG, n=10) and toxic nodular goiter (TNG, n=10).
Methods: GPR-39 and GHSR in thyroid tissues were detected by immunohistochemistry & Western Blot, while preproghrelin by RT-PCR.
Results: We revealed higher expression of both proteins in GD patients (+++; ++) in comparison with NTNG (+;+) and TNG patient(++,+). GPR-39 was present in thyroid autoimmune disease, NTNG and TNG at band p51(kDa). The ghrelin receptor was identified in all study groups at p70. mRNA expression for preproghrelin was found in thyroid tissues from patients with immune and non-immune thyroid diseases.
Conclusions: We conclude that the expression of the ghrelin receptor family in thyroid tissues may suggest a role of gastric peptides in thyroid functions. mRNA of preproghrelin expression is a proof of ghrelin-gene derived peptides presence in thyroid tissue.

P1-d2-600 Thyroid 2

Predictors of malignancy in paediatric thyroid nodules

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Background: Clinical, laboratory, and imaging data are employed to assess the likelihood of malignancy of pediatric thyroid nodules selecing patients needing a Fine-Needle Aspiration Biopsy (FNAB). The latter represents the gold standard for discriminating benign and malignant nodules.
Objective: Evaluate the diagnostic accuracy of clinical, laboratory, and imaging predictors in children with malignant and benign thyroid nodules.
Methods: Data of 116 consecutive patients with thyroid nodules ≥1 cm submitted to FNAB have been retrospectively evaluated and compared with respective cyto/histologic outcome. Differences between malignant and benign nodules were assessed by Fisher exact or Student t tests. A linear binary regression model was designed to assess the factors predictive of malignancy.
Results: Thirty-four patients had tumoral nodules: 22 papillary cancer, 8 follicular adenoma, 3 Hurtle-cell carcinomas, 1 medullary carcinoma, all histologically confirmed after thyroidectomy. Eighty-two patients had benign "goitrous" nodules based on histology (17 cases) or benign cytology plus at least 1 year follow-up. When compared with those with benign nodules, patients with malignant ones were more likely males with a solitary nodule with irregular margins, had more frequently palpable lymph nodes, microcalcifications, an hypoechoic nodular pattern, an increased intranodular vascular flow, sonographic lymph nodal alterations, and a higher serum TSH at FNAB. The regression analysis defined as predictors of malignancy microcalcifications, increased intranodular vascular flow, sonographic lymph nodal alterations, and serum TSH concentration (Table).
Conclusions: Microcalcifications, increased intranodular vascular flow, lymph nodal echographic alterations and serum TSH at FNAB are strongly associated with malignant thyroid nodules in pediatrics. There parameters may be employed as predictors in order to select patients needing further investigations and surgery.

P1-d2-601 Thyroid 2

Thyroid disease in children with PTEN Hamartoma tumor syndrome: when should we start to screen?

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Background: PTEN Hamartoma tumor syndrome (PHTS) is caused by a mutation of the PTEN tumor suppressor gene. Patients with PTEN Mutation have an increased risk to develop benign and malignant tumors of breast and thyroid, but also intestine and skin. To date there are no evidence-based recommendations for diagnostic workup and cancer surveillance for children.
Objective: To develop screening recommendations for thyroid cancer surveillance in children with PTHS.
Methods: Medical records and if available thyroid histology of children with PHTS presenting in our clinic as well as current literature were reviewed to evaluate the risk for thyroid disease at an early age of life.
Results: In all children mutation analysis was performed because of a combination of macrocephaly, delayed psychomotor developmental in combination with other features (e.g. lipoma, family history). 4 of 7 patients with PTHS followed up in our clinic exhibited thyroid disease at an early age (4 - 9 years). All patients were screened by thyroid ultrasound after confirmation of PTEN mutation. In 3 patients, thyroid ultrasound showed a complex nodule. To date, thyroidectomy was performed in two patients. Histology revealed a thyroid adenoma without malignancy in both cases.
Conclusions: Children with PTEN mutation develop thyroid disease at an early age. Thyroid cancer is frequently reported in adults with PTHS; however one study reported 5 children who developed thyroid cancer between the age of 6 and 12 years. Thus, based on our and other's experience we recommend annual ultrasound surveillance for thyroid disease in all patients with diagnosis of PTEN mutation, regardless of their age to enable early intervention in suspicious cases.

P1-d2-602 Thyroid 2

Evaluating the cognitive functions in subclinical hypothyroidism by P300 event related potential

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Background: P300 wave is an event related potential (ERP) component which is associated with the process of decision making. Influences of mild sub clinical hypothyroidism (SH) on cognitive function and the necessity of treatment are still controversial issues.
Objective and hypotheses: The aim of this study is to compare the cognitive functions of children with SH, before and after treatment by neuropsychological tests and an objective neurophysiologic method like P300.
Methods: The patients who were diagnosed with SH (TSH: 5-10 μIU/L) between the ages of 9-18 years, and had no chronic systemic diseases were included to the study (n=15). They were treated with L-thyroxine after the first assessment by P300 and neuropsychiatric tests which evaluate attention, perception, recent and remote memory. The patients were reevaluated after 6 months of treatment. Similar neuropsychiatric tests were performed to the control group (n=20) and the results were compared.
Results: Pretreatment verbal memory (VM) and verbal recall (VR) scores of the study group were significantly lower than the control group (p= 0.004 and

0.012 respectively). However there were no significant difference between the posttreatment and control groups (p>0.05). Posttreatment VM and VR scores were significantly higher than the pretreatment scores (p=0.008 and p=0.0001). There were not any significant difference between the pre- and posttreatment values of N1, P2, P3 latencies or P3 amplitude (p>0.05), although there was a significant decrease in N2 latency (p=0.03). Negative correlations were determined between the pretreatment TSH values and mean VM and VR scores of the study group (p=0.015, r=-0.38 and p=0.047, r=0.31).
Conclusions: This study shows that there are some alterations in central nervous system functions in the SH patients The increase in visual and verbal memory scores besides the decrease in N2 latency are interpreted as the benefits of the treatment in these patients.

P1-d2-603 Thyroid 2

Cognitive outcome in congenital hypothyroidism and initial L-thyroxin dose:

a meta- analysis

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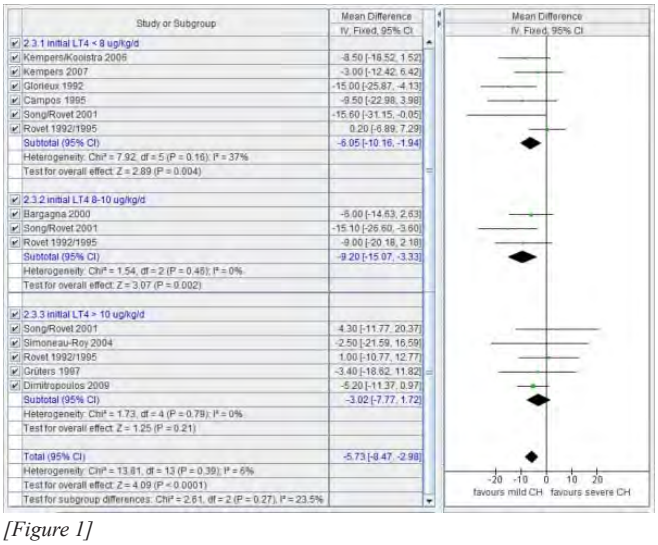
Background: There is no evidence based consensus on initial LT4 dose for children with congenital hypothyroidism (CH). Contradictory data have been published on the effect of higher doses above 10µg with some concern that an overdosing might be harmful.
Objective and hypotheses: So far no meta-analysis of published studies to asses the overall impact of the initial L-Thyroxin dose on the cognitive outcome in children with CH of different severity has been conducted.
Methods: We performed a meta- analysis using published data and available raw data to determine the effect of initial LT4 dose on the cognitive outcome (defined as IQ) in children with severe vs. mild CH (defined by initial T4 or fT4 values). In a systematic search in PUBMED and reference lists of published papers eleven cohorts that met the inclusion criteria have been selected. Cohorts were divided into three groups: treated with low (< 8), median (8-10) and high initial LT4 dose (>= 10µg/kg/day). We calculated mean IQ and SD for each severity group per cohort and plotted them for all included cohorts using the 5.1 version of the Review Manager (Fig.1).
Results: An initial LT4 dose of < 8 and 8-10 µg/kg/day results in a significantly lower intellectual outcome in severe vs mild CH (6 IQ points, p= 0.004 and 9 IQ points, p= 0.006 respectively). With a higher LT4 dose a statistically non- significant difference of 3 IQ points between the severity groups was present (p= 0.21).



[Figure 1]

Conclusions: High initial LT4 starting dose seems to close the intellectual gap between severely and mildly affected children with CH and does not lead to any oposite IQ outcome in the mildly affected children excluding an overdosing- hazard.

P1-d2-604 Thyroid 2

Should we treat euthyroid children with autoimmune Hashimoto-thyroiditis (HT) with levothyroxine (LT4)? Results of a multicenter,

randomised, controlled clinical trial

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Background: The benefit of L-T4 treatment of euthyroid children with Hashimoto thyroiditis (HT) is still a controversial issue.
Objective: To determine the effects of L-T4 treatment on thyroid gland volume, thyroid antibodies, and TSH and fT4 levels in euthyroid subjects with HT.
Design: We conducted a prospective, randomized, open, controlled clinical trial at 10 tertiary care centers for pediatric endocrinology in Bavaria and Baden-Württemberg. Our intention was to study 120 euthyroid HT patients; 60 with L-T4 and 60 without L-T4, during an observation period of 60 months. Due to various reasons the overall aims of the study were not achieved and the study was terminated earlier than planned. Patients:59 patients met the inclusion criteria. Of these, 25 patients (21 f, 4 m; age: 11.8±2.3 yr.) were randomized to receive L-T4, and 34 patients (27 f, 7 m; 12,6±1.2 yr.) were not treated. The patients who developed hypothyroidism (n=13) were removed from the observation group. L-T4 (1.6 µg/kg daily) was given for 36 months in the treatment group. Thyroid gland volume (by ultrasound), serum levels of TSH, fT4, TPOAb, and TgAb were assessed every 6 months for 36 months.
Results: Mean thyroid volume decreased in the treatment group from 2.5 SDS (start) to 1.9 SDS after 36 months, and in the observation group from 1.6 to 1.1 SDS. Between both groups, thyroid volume was statistically not significant different. Mean TSH decreased (from 3.0 to 1.7 mU/L), and fT4 increased significantly (from 12.3 to 15.6 pg/ml) in the treatment group after 6 months. TSH and fT4 levels were significantly different between both groups only at 12 months (p< 0.05). TPOAb levels were not significantly different in both groups during the entire study period, whereas TgAb levels were lower in the observation group right from the start.
Conclusions: In euthyroid HT patients, L-T4 treatment did not reduce thyroid volume and had no effect on thyroid function and serum autoantibody levels.

P1-d2-605 Thyroid 2

High prevalence of single gene mutations in severe congenital hypothyroidism

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Background: The prevalence of single gene mutations in congenital hypothyroidism (CH) remains undetermined.
Objective and hypotheses: The objective of this study was to determine the prevalence of gene mutations in *DUOX2*, *TSHR*, *TG*, *PAX8*, and *TPO* among severe permanent primary CH patients in our institute.
Methods: Between April 1999 and March 2011, a total of 114,733 newborns were screened for CH in our region. Among them, 330 newborns were suspected of CH and referred to pediatricians. We recruited 40 patients who were referred to our institute. Of these, 27 patients were diagnosed with or suspected of having permanent primary CH and enrolled in this study. From these 27 CH patients, we extracted nine severely affected patients with initial TSH ≥ 20 mU/l at newborn screening and performed direct sequencing of the five candidate genes.
Results: Three of nine patients (33%) had mutations in *PAX8*, *TPO*, and *TSHR*. The identified *PAX8* and *TPO* mutations were novel, while the *TSHR* mutation has been shown to be common in our country. In the severely affected subjects, 60% of patients had thyroid dysgenesis (TD), while in patients with initial TSH at newborn screening < 20 mU/l, only 12% had TD.
Conclusions: In spite of the high TD frequency, the prevalence of single gene

mutations among severe permanent primary CH patients in our institute was higher than expected. This study suggests that the genetic analysis of five genes, namely, *DUOX2*, *TSHR*, *TG*, *PAX8*, and *TPO*, is useful and the actual prevalence of gene mutations among CH patients is higher than previously estimated.

P1-d2-606 Thyroid 2

High blood TSH values in newborns hospitalized in NICU

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Background: Previous studies have reported the spectrum of thyroid function abnormalities in critically-ill neonates showing transient hypothyroxinemia and sick-euthyroid syndrome to be common in these infants. Moreover, many postnatal factors have been demonstrated to be associated with these conditions. However no large studies have been conducted to evaluate a possible association between higher neonatal TSH levels at screening and postnatal factors in NICU hospitalized newborns.
Objective and hypotheses: The aim of this study was to evaluate the neonatal TSH levels at screening and the risk of congenital hypothyroidism (CH) in infants hospitalized in NICU.
Methods: Preterm newborns with GA = 34-36 w admitted to NICU (n= 163) and nursery (NURS, n=374) of Mangiagalli Clinic, Milan, in the year 2008 were considered for the study. Blood TSH (BTSH) levels at screening and re-screening in NICU newborns were compared with those observed in NURS babies. The prevalence of CH was also evaluated in both groups of newborns.
Results: The BTSH median values found in NICU babies at screening were similar to those observed in NURS babies (1.6 vs 1.7 mU/L), whereas at re-screening BTSH median values were significantly higher in NICU (1.5 mU/L at 10-20 days and 1.7 mU/L at 21-31 days) than in NURS babies (1.2 mU/L at 10-20 days and 1.0 mU/L at 21-31 days; P< 0.05 for both comparisons). The frequency of CH was 2.4% (4/163) among NICU babies (1 hypoplasia and 3 in situ thyroid) and 0.2% (1/374) among NURS babies (in situ thyroid).
Conclusions: Our preliminary results showed that NICU babies had significantly higher values of BTSH at re-screening and higher frequency of CH than NURS babies with the same GA. Therefore, perinatal and postnatal factors associated with NICU hospitalization may have a role in thyroid deficiency in these babies.

P1-d2-607 Thyroid 2

When is it justifiable to await venous thyroid function tests before starting thyroxine treatment in infants referred with capillary TSH elevation?

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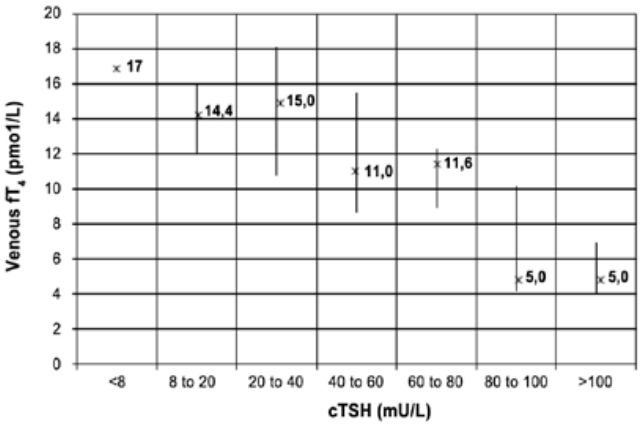
Background: In Scotland median (range) age at notification for elevated neonatal capillary (c) TSH is 10 (3-35) days. If cTSH elevation is >100 mu/L, decompensated hypothyroidism is likely and thyroxine treatment should start without delay. However, if TSH elevation is mild the clinician may prefer to wait for the venous fT4 result which may be normal rather than commit the child to 2-3 years of thyroxine.
Objective: To determine if there is a cTSH threshold which is predictive of a fT4 ≤10 pmol/L.
Methods: Data was analysed from all TSH referrals by the Newborn Screening service from 2002 when assay and cut-off TSH values were last changed.
Results: 254 infants were suitable for study and were included in the statistical analysis. Of these, 169 had definite/probable hypothyroidism, 42 had transient TSH elevation and 41 were of uncertain thyroid status. A direct comparison between cTSH and venous fT4 demonstrated a correlation of -0.61 (p< 0.0001). A ROC curve analysing cTSH as an indicator of fT4 < 10 confirmed this as a strong predictor (area under the curve = 0.891, p< 0.0001).



[Figure 1]

Figure 1 shows average fT4 result by TSH group. Mean fT4 levels are frankly low with cTSH >80 mU/L, borderline low with cTSH 40-80 mU/L but normal with cTSH < 40 mU/L.
Conclusions: There is a excellent correlation between the current method used for cTSH screening and confirmatory venous fT4 results. A cTSH of ≤40 mU/L gives a ~10% chance of fT4 being < 10 pmol/L. As such, if an infant presented with a cTSH of ≤40 mU/L with no clinical features of hypothyroidism, a clinician would be justified in awaiting venous fT4 results before committing that infant to long-term thyroxine treatment.

P1-d2-608 Thyroid 2

Abstract has been withdrawn

P1-d3-609 Thyroid 3

Subclinical hypothyroidism in *in vitro* fertilisation babies

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Background: Assisted reproduction technology has become a treatment of choice for infertility and is used widely on clinical grounds, but neonatal morbidity and mortality risks in IVF pregnancies have not been satisfactorily evaluated yet. There is a great concern about the morbidity of in vitro fertilization (IVF) babies, but investigations were mostly related to mechanical conditions that were attributed to multiparity.
Objective and hypotheses: We aimed to investigate thyroid functions of newborn babies conceived with IVF compared with the control group.
Methods: A total of 98 healthy, term IVF newborns were evaluated between postnatal 2 to 4 weeks of age by screening of thyroid function between July 2006 and April 2008. Ten subjects were assessed as a study group whose TSH levels were higher than 6.5 mU/L. Control group consisted of randomly selected 10 naturally conceived infants with hyperthyrotropinemia (whose TSH levels were higher than 6.5 mU/L but under 15 mU/L) with the same age. All children were thoroughly examined, and serum fT4, TSH, anti-thyroid peroxidase, anti-thyroglobulin antibodies were measured and a TRH test was performed in all subjects in both groups.
Results: Euthyroid hyperthyrotropinemia was diagnosed in approximately 10 % of IVF babies. Exaggerated TSH levels to TRH were obtained in all IVF

babies (subclinical hypothyroidism) but in none of the controls. A significant difference was noted in the concentration of TSH at the 20 th min between the two groups ($p< 0.001$). Besides, sustained and delayed TSH responses were observed in IVF babies. Neonatal screening tests were negative in both of the groups.
Conclusions: In IVF babies, despite normal neonatal screening tests, subclinic hypothyroidism in about 10% of IVF newborns. Therefore, screening and follow-up procedures should take this risk into account in newborns conceived with IVF.

P1-d3-610 Thyroid 3

High prevalence of positive anti-thyroid antibodies, low serum thyroid hormones and high serum TSH associated with a low vitamin D (VitD) status in a paediatric cohort

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Background: Observational studies have demonstrated the association of VitD status with a number of common disorders which have been described as non-classic effects of VitD. VitD is well recognized as an immunomodulator and VitD insufficiency has been associated with autoimmune thyroid disease. Chailurkit et al (2013) have described that a high VitD status in younger individuals is associated with low circulating TSH. It is unclear, how VitD status is related to TSH levels in the pediatric population.
Objective: Our aim was to study the association between VitD status and anti-thyroid antibodies, serum thyroid hormones and serum TSH in a pediatric cohort.
Methods: We selected 153 patients (57 boys 37%, 96 girls 62%) with ages ranging from 1 month to 18 years, with Calcium(Ca), Phosphorus(P), Parathyroid hormone(PTH), and Alkaline Phosphatase(ALP) values within the normal range. Thyroid function was assessed with thyroid hormones (T3, T4, and fT4), TSH and anti-thyroid antibodies (ATPO and UATG). Ca, P, and ALP were assessed by Cobas 511, Roche. PTH, UATG and ATPO by Immulite 2000, Siemens. VitD, thyroid hormones, and TSH by Architect i2000, Abbott.
Results: We have found a statistically significant positive correlation between levels of VitD (ng/ml) and T3 (ng/ml) (T3= 1.2843+0.0062xVitD, r: 0.71, $p< 0.019$;); T4 (µg/dl) (T4= 6.9663+0.0267xVitD, r: 0.62, $p< 0.049$) and FT4 (ng/dl) (FT4= 1.0702+0.0042xVitD, r: 0.80, $p< 0.006$) and a statistically significant negative correlation between VitD and TSH (µIU/ml) levels (TSH= 4.1721-0.0488xVitD, r: 0.75, $p< 0.018$). The presence of thyroid antibodies was statistically significantly higher in the group of severe deficiency of VitD (between 10-20, 53.3% positive) than in the deficient (VitD 20-30, 35.9%) and normal group (VitD 30-80, 25.0%).
Conclusions: According to previous reports these results suggest that VitD might have also an immunomodulator effect on thyroid function in a pediatric cohort.

P1-d3-611 Thyroid 3

Functional characterization of a novel iodide transport defect (ITD) causing Na^+/I^- symporter (NIS) mutation

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Background: ITD is an uncommon cause of dyshormonogenetic congenital hypothyroidism that results from inactivating mutations in the NIS gene. Clinical manifestations include low to absent thyroid and salivary iodide uptake and variable degrees of hypothyroidism, goiter, and mental retardation.
Methods: Index patient presented at 7 3/12 years of age with severe primary hypothyroidism, growth failure and delayed bone age. Thyroid autoantibodies were negative. US showed a multinodular gland. Thyroid uptake scan demonstrated a decreased uptake of 5.4% and absent uptake in salivary glands. Her sibling, at 2.5 years, showed mild hypothyroidism. The genomic DNA encoding NIS was sequenced in the 2 sisters and parents, and in vitro functional studies of a newly identified NIS mutation were carried out.
Results: Both patients were compound heterozygous for mutations R124H/V270E. The R124H NIS mutant has previously been identified as a cause of ITD. The newly identified V270E NIS mutation caused a substantial decrease in I^- uptake when expressed in COS-7 cells. Flow cytometry revealed a severe impairment in targeting of V270E NIS to the plasma membrane. Strikingly, membrane vesicles from V270E NIS-expressing cells transport I^- approximately as much as vesicles from wild-type NIS-expressing cells, indicating that, although trafficking of V270E NIS to the cell surface is impaired, the protein itself is highly functional. V270D also resulted in intracellular retention, indicating that a negative charge is not tolerated at position 270. Remarkably, V270Q NIS is targeted to the cell surface.
Conclusions: We demonstrate that the V270E substitution reduces NIS targeting to the plasma membrane in two patients with congenital hypothyroidism, thus causing a decrease in I^- uptake even though V270E NIS is intrinsically active. This may explain the unusual phenotype in the 7yr old index patient, who despite severe hypothyroidism is intellectually normal.

P1-d3-612 Thyroid 3

Capacity building and training of personnel for congenital hypothyroidism screening in Nigeria

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Background: Screening for congenital hypothyroidism has been established for over 5 decades in many industrialised nations even though the incidence has remained at 1 in 3000 - 4000 live birth. Though there is iodine deficiency in some parts of NIgeria, no congenital hypothyroidism screening programme has been initiated. For this reason, ESPE trained Paediatric Endocrinologists in Nigeria decided to conduct a pilot study for congenital hypothyroidism screening.
Objective: To train personnel on how to collect cord and heel blood for screening for CH,
Methods: ESPE trained Paediatric endocrinologists in different parts of the country were asked to nominate nurses and midwives from the obstetric units of their hospitals for training on cord and heel blood sampling for CH. Two (2) different sessions were held in 2 major cities in Nigeria covering all 6 geopolitical zones. Three resource persons (O B, A P, Y I) conducted the training, and placenta cord and Hartmann protein savers were used to collect the blood and stored in cool dry place. The training took 2 hours in each center.
Results: 21 medical doctors with 28 midwives were trained on sampling techniques and data collection. Trainees and trainers discussed methodological and logistic problems that may arise and proffered solutions to these. These trained personnel are also charged with the responsibility of training other health care workers in their various institute to scale up the numbers for effective coverage of the entire country.
Conclusions: Training midwives and doctors in skills necessary for blood sampling for CH will improve scale up and this model can be used in other African countries until every country starts and sustains CH screening of newborns.

P1-d3-613 Thyroid 3

The effect of thyroxine treatment during the first two years of life in children with Down syndrome on development and growth at the age of 10.7 years

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Background: A high percentage of young infants with Down syndrome (DS) have subclinical hypothyroidism, which may contribute to their suboptimal brain development and growth. In a randomized placebo controlled trial thyroxine (T4) treatment during the first two years of life resulted in small improvements in motor development and growth at the age of two years, and a tendency towards improvement in mental development.
Objective and hypotheses: The aim of our study was to examine whether these effects on motor (and mental) development and growth of T4 treatment in infants with DS persists over time.
Methods: We invited children who completed the original trial (n=181) for a single follow-up visit at the age of 10.7 years. A blinded psychologist assessed motor and mental development using validated developmental tests. Trained and blinded medical students supervised by a pediatric endocrinologist assessed growth and puberty. The measurements in the T4 and placebo groups were compared using unpaired T-tests or Mann-Whitney U tests for continuous data, and Chi-square tests for dichotomous variables.
Results: We included 123 children (follow-up rate 68%). 52% was treated with T4 in the original trial and 52% was male. We found no difference between T4 treated and placebo treated children in motor development (p=0.92), motor coordination (p=0.52) or mental development (p=0.73).
T4 treated children had a larger head circumference (mean difference 0.6 cm, 95% CI 0.4 to 1.1) and tended to be taller than placebo-treated children (mean difference 2.1 cm, 95% CI -0.1 to 4.2). Mean weight did not differ between groups (p=0.43).
Conclusions: These results suggest that T4 treatment in children with DS during their first two years of life does not lead to better motor or mental development at the age of 10.7 years compared to placebo treatment. Yet, early T4 treatment seems to have a lasting effect on physical growth.

P1-d3-614 Thyroid 3

Mutations in the TTF1 and the PAX8 genes in a boy with thyroid dysgenesis, respiratory and neurological disorders

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Background: Among genetic factors that may contribute to thyroid dysgenesis (TD) the highest importance is ascribed to mutations in genes which encode for transcription factors. In the majority of cases no mutations can be detected in patients with TD. This may be due to the fact that the thyroid phenotype varies (hypoplasia, aplasia or dysplasia).
Objective: We describe a patient with TD, respiratory disease and cerebral palsy and who has two heterozygous mutations in the *PAX8* (p.E234K) and the *TTF1* (p.A329GfsX108) genes. *In vitro* studies were performed to functionally characterize these mutations.
Patient: The 12 years-old boy was diagnosed to have congenital hypothyroidism (CH) at neonatal screening, with a serum TSH of 49.5 mU/L (N: 0.4-9) and a T4 of 3.76 µg/dl (N: 50-197). The thyroglobulin value was 3.18 ng/ml, N< 55 and hypoplastic thyroid in ultrasonography. After birth, he developed severe respiratory failure, seizures and an ischemic cerebral infarction. He was diagnosed with cerebral palsy and symptomatic epilepsy and developed a considerable psychomotor retardation. Currently he is euthyroid under L-thyroxine supplementation. His sister and the parents are healthy and euthyroid.
Methods: We introduced the two identified mutations into expression vectors and transiently transfected them into HeLa cells. In EMSA studies we tested for the DNA binding capability of the two mutated transcription factors.
Results: The PAX8 mutation was normally located to the nucleus and showed a normal transactivation of and normal binding to the known downstream targets. In contrast the TTF1 mutation did not show any transactivation ability. It remains to be elucidated whether the TTF1 mutation can bind to DNA or localize to the nucleus.
Conclusions: The *TTF1* mutation might be responsible for the phenotype observed in our patient. The synergistic effect is completely abolished by the TTF1 mutation when cells were co-transfected with the PAX8 expression constructs.

P1-d3-615 Thyroid 3

Ectopic intrathyroid thymus in childhood: a sonographic finding leading to misdiagnosis

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Background: During gestation, the primordial thymus migrates from the pharynx to the anterior mediastinum and thymic tissue can remain at any point along this path. Intrathyroidal thymic remnants are considered rare and their sonographic patterns are only recently described in small case series.
Purpose: To present the sonographic appearance of ectopic intrathyroid thymus and to emphasize the role of sonography to avoid misdiagnosis and errors in management.
Methods and subjects: 42 children, 3.5 - 14 years old, were involved in this retrospective study. They were referred for a sonographic examination of the thyroid gland due to positive family history or symptoms indicative of thyroid disease.
Results: A fusiform intrathyroidal lesion, with no mass effect, homogeneously hypoechoic, with diffuse bright internal echoes, was demonstrated. The similarity to the characteristic sonographic pattern of the normal mediastinal thymus was crucial for the diagnosis of ectopic intrathyroidal thymic tissue. In 8 cases, a normal elongated thymus was found connected to the thyroid with an accessory lobe embedded in the lower thyroid pole. The above sonographic appearances mimicked a thyroid nodule.
Based on their similarity to the normal thymus echotexture, and their geographic distribution, it was decided not to proceed with any further investigation, recommending close sonographic follow-up. Repeat sonograms at 6 and 12 months in 32 children, confirmed the stability of the sonographic findings, whereas in 4 adolescents the size of the intrathyroid thymus gradually decreased.
Conclusion: Awareness of the sonographic patterns of the ectopic intrathyroidal thymus is mandatory to avoid misdiagnosis. We believe that further investigation is unnecessary and sonographic follow-up should be recommended.

P1-d3-616 Thyroid 3

Subclinical hypothyroidism in childhood: presentation modes and evolution over time

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Background: Most experts agree that subclinical hypothyroidism (SH) represents early, mild thyroid failure, however there are controversies about the evolution of SH over time.
Objective and hypotheses: The aim of the study was to analyze the dynamics of thyroid dysfunction in children initially referred as patients with SH. During the period 2010-2012, 258 unselected consecutive SH patients (140 girls and 118 boys) were studied in one clinical center.
Methods: Thyroid examination (clinical and ultrasound), laboratory tests (TSH, fT4, fT3, anti-TPO, anti-TG Ab) were carried out at least once in each patient.

Results: The mean age at SH diagnosis was 7.30 yrs (SD 5.44, medium 7.09 yrs; .range: 0.0 - 17.86 yrs). SH girls were older than boys but not significantly (7.66+/-5.51 v 6.89+/-5.34; p=NS). In 25 (9.6%) patients there was positive family history. On the basis of follow-up study it was found that out of 258 SH patients, 17 (6.5%) had positive thyroid autoantibodies and Hashimoto thyroiditis was diagnosed. Six (2.3%) patients developed hypothyroidism, but only in one of them TSH levels were below 10 mU/l initially.
Conclusions: Our data confirmed that only a small percentage of children with SH can proceed to overt hypothyroidism.

P1-d3-617 Thyroid 3

Natural regulatory T cells: CD4 FoxP3 and CD8+CD122+ T in children with autoimmune thyroiditis

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Background: Tregs play an important role in autoimmune pathogenesis by maintaining self-tolerance and the control of effector cells. CD4+Foxp3+ T cells are well known naturally occurring Tregs.Recently CD8+CD122+ T cells were also described as Treg cells.
Objective and hypotheses: Of the study was to evaluate the subsets of naturally occurring Treg CD4+FoxP3 and Treg CD8+CD122+ in children with autoimmune thyroiditis (AIT) and the expression of regulatory molecule CTLA-4 in this subsets.
Methods: 42 children were examined: 27 with chronic autoimmune thyroiditis type Hashimoto, mean age 12.7±3.8 years and 15 healthy children as controls. PBMCs were stained with monoclonal antibodies according to manufacturer instructions. First tube: anti-CD25 PE-Cy7, clone M-A251; anti-CD4 APC-Cy7; anti-CD127 PE, anti-CD152 APC and intracellular anti-FoxP3 Alexa Fluor 488, clone 259D/C7 (Becton Dickinson); second tube: anti-CD8 FITC, anti-CD122 PE, anti-CD152 APC (Becton Dickinson). Isotypic controls were included. The samples were evaluated using flow cytometer FACSCanto II (Becton Dickinson). TSH, thyroid hormones and thyroid antibodies were evaluated by MEIA, Abbott.
Results: Children with AIT have statistically significantly lower percentage of Tregs CD4+FoxP3 than healthy children 1.58±0,8 *vs* 2,58±1,4, respectively (p=0.03). The percentage of CD8+CD122+ did not differ in AIT children and in control group. The percentage of Tregs expressed antigen CD152+ was similar in children with AIT and in control group in both Treg subsets examined in the study. In children with AIT were not found any significant correlations between Tregs percentage and hormonal or antibodies status.
Conclusions: Children with AIT have decreased value of CD4+FoxP3+ Tregs, but the percentage of other regulatory subset, CD8+CD122+ T cells does not differ in comparison to healthy children.

P1-d3-618 Thyroid 3

Molecular basis and oligogenic causes of permanent and transient congenital hypothyroidism with enlarged- or normal-sized eutopic thyroid glands

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Background: Congenital hypothyroidism (CH) is the most common inborn endocrine disorder and preventable cause of mental retardation. About 15% of cases are associated with enlarged- or normal-sized eutopic thyroid glands.
Objective: This study aimed at molecular and functional characterization of transient or permanent CH with enlarged- or normal-sized eutopic thyroid glands.
Methods: The study included 50 transient or permanent unrelated CH patients (33 males and 17 females) with normal-sized or enlarged eutopic thyroid. Goiter was observed in 15 patients. All patients except of two patients with low thyroglobulin (TG) were tested for mutation analysis of *DUOX2*, *TPO* and *TSHR* genes. Additional *TG* gene analysis was done in two patients with extremely low TG. For novel variants of *DUOX2*, functional defects were evaluated by measuring H_2O_2 generation *in vitro*.
Results: Twenty three of 50 (46%) were determined to have transient CH, and 27 of 52 (54%) were turned out to be permanent. *DUOX2* variants were identified in 26 out of the 50 patients (52%). Eleven patients showed biallelic variants, and 15 patients carried monoallelic mutations in *DUOX2*. Four patients with *DUOX2* variants also harbored *TSHR* mutations (p.R450H, p.G132R, p.L13I). Among 24 patients without *DUOX2* variants, two patients with low or absent uptake on scintigraphy had compound heterozygote mutations of TSHR gene. Two patients harbored heterozygous p.R351L mutations in *TPO*. *TG* gene analysis revealed one heterozygote mutation and one homozygote variants.
Conclusions: This study indicated that *DUOX2* mutation is the most common cause of transient or permanent CH. The phenotypic variability of patients with *DUOX2* mutation could be explained by oligogenicity, epigenetic changes, and ethnic or environmental differences. Further studies are required to explain alternative mechanisms of compensation for the loss of DUOX2 function or influencing factors of DUOX2 expression in order to understand phenotypic diversities.

P2-d1-619 Adrenals and HPA Axis 4

Molecular and phenotypical characterisation of ten families with 11ß-hydroxylase deficiency

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Background: 11ß-hydroxylase deficiency (11-OHD) is the second most common cause of congenital adrenal hyperplasia and it is caused by *CYP11B1* gene mutations. It is characterized by genital ambiguity in affected girls and precocious pseudopuberty in both sexes. Hypertension can occur in about two thirds of patients. The non-classic form of 11OHD is manifested by signs of androgen excess during childhood.
Objective and hypotheses: To characterize the *CYP11B1* gene alterations of these patients.
Methods: Herein we report 7 patients with classical and 4 with non-classical 11-OHD, selected for high hormonal levels of 11-deoxycortisol measured by ID-LC-MS/MS or for negative analysis of the *CYP21A2* gene. The entire *CYP11B1* gene was sequenced and four mutations were functionally characterized (paper submitted).
Results: 8 novel putative mutations were identified: 5 missense mutations (p.R143W, p.E310K, p.V316M, p.R332Q, p.Q337P), 2 splicing mutations (g.-1 IVS6 G>C, g.+148 IVS5 C>G) and one non sense mutation (p.R384X). Furthermore 5 already reported mutations were identified (p.L299P, p.A306V, p.T318R, p.Q356X, exon 7 g.ins4566-4567 GA). By *in vitro* studies, the p.E310K and the p.A306V resulted to be severe mutations causing classical 11-OHD; instead the p.R143W and the p.R332Q, with a higher residual activity, resulted milder mutations. In a pair of brothers with non classical 11-OHD due to the same *CYP11B1* mutations, the boy showed an earlier manifestation of the symptoms, that may be due to an additional intron 2 splice site mutation in the *CYP21A2* gene.
Conclusions: The detection of patients with non classic phenotypes underscore the importance to screen patients with a phenotype comparable to non classic 21OHD for mutations in the *CYP11B1* gene in case of a negative analysis of the *CYP21A2* gene. As *CYP11B1* mutations are most often individual for a family, the in vitro analysis of novel mutations is essential for clinical and genetic counselling.

P2-d1-620 Adrenals and HPA Axis 4

Premature adrenarche and glucocorticoid sensitivity

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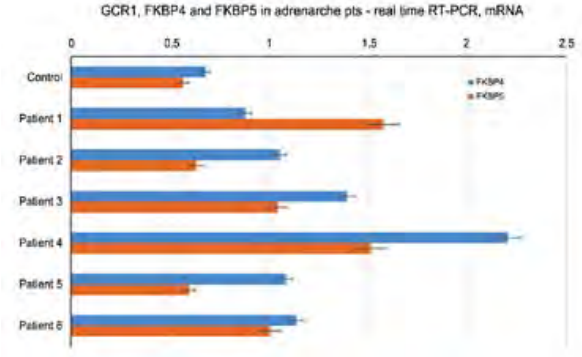
Objective: Determine glucocorticoid sensitivity (GS) in Premature adrenarche (PA) and genes associated.
Methods: 18 children with PA and 18 controls were evaluated for glucocorticoid sensitivity. In addition random five PA cases were subjected to mRNA expression study by real time RT PCR and sequencing of *FKBP4*, *FKBP5* and *NC3R1* genes for mutations. Fluorinated dexamethasone (F-Dex) binding monocyte binding studies used to determine GS.
Results: Seven of thirteen (54%) patients with PA had decreased F-dex binding. Three patients had increased GC sensitivity (23%) and three other were not different from control. *FKBP4* gene variant is present in up to 30% of the general population and was associated with inhaled therapy of steroids in asthma. *FKBP5* gene variant is present in up to 60% of the general population and it was associated with outcome of stress and child abuse and mood disorders. *NR3C1* gene variant is present in up to 24% of the population and was associated with chronic fatigue and depression. At this time none of the described genetic variants was shown to have clinical relevance to PA. Real time PCR results shown in table 1. NR3C1 mRNA expression are pending.
Conclusions: Data suggest PA is associated with abnormal GC sensitivity. FKBP4 and FKBP5 may be largely involved in pathogenesis of PA. We can speculate that this phenomenon may lead to increased susceptibility and vulnerability of the described genes to DNA damage or modulated epigenetic regulation and inappropriate inhibition/activation. Regardless of the mechanisms, our functional studies of glucocorticoid receptor identified impaired GC sensitivity in PA. However exact mechanism still unclear.



[Table 1]

P2-d1-621 Adrenals and HPA Axis 4

Optimisation of hydrocortisone treatment in children with hypopituitarism using 24 hour serum cortisol profiling

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Background: The aim of therapy in ACTH deficiency is to replace glucocorticoids in a physiological pattern at the lowest effective dose. Marked variability exists in hydrocortisone (HC) metabolism among individuals, resulting in the need for individual assessment and titration of treatment.
Objective and hypotheses: We evaluated the use of cortisol profiles in patients with (suspected) hypopituitarism with and without HC treatment to optimise treatment.
Methods: We constructed 24h serum cortisol profiles by drawing blood samples at 2h intervals for 24h in 81 children with hypopituitarism on HC (group A, mean age (SD) 7.12 (4.5) yr) and in 51 children (group B, mean age 7.09 (4.0) yr) who had not as yet received HC. After profiling, 13 patients of group B were started on HC (B1) and 38 were not (B2).
Results: Mean (SD) 24h cortisol concentrations were higher in the HC-treated children compared to non-treated children (A: 220.4±107.4 vs B: 177.7 ± 50.3 nmol/l, $p< 0.05$) but not compared to those that remained off HC treatment (B2: 193.6±47.9 nmol/l). Mean HC dose was 15.8±5.0, 10.6±3.1 and 9.6±3.3 mg/m^2/d in infants, prepubertal and pubertal children respectively. Children on HC had more frequent low (< 50 nmol/l) and high (>700 nmol/l) cortisol concentrations ($p< 0.05$ group A vs B2).
BMI SDS, but not height SDS, was higher in the HC-treated group (A: 1.41 ± 1.7 vs B2: -0.07 ± 1.3, $p< 0.0001$). HC-treatment was adjusted in 54% of patients, with a dose increase (21%), dose decrease (14%), change in frequency (9%) or change in timing (19%).
Conclusions: In children with hypopituitarism receiving HC treatment, cortisol profiling demonstrated greater mean cortisol concentration, but frequent supraphysiological peaks or suboptimal troughs. Profiling may aid in the adjustment of treatment leading to a more physiological cortisol exposure. The increased BMI in these children is a further reason to aim for the most physiological HC replacement.

P2-d1-622 Adrenals and HPA Axis 4

Paediatric reference intervals for FSH, LH, estradiol, testosterone, DHEA-S and cortisol by electrochemiluminescence

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Background: The gonadotropin and steroid values obtained in various laboratories are often not comparable because of methodological differences. It is important to have normal data that are specific for the methods being used in the laboratory performing the test.
Objective and hypotheses: To determine the reference values for FSH, LH, estradiol (E2), testosterone (To), DHEA-S and cortisol in our population pediatric.
Methods: 693 healthy neonates and infants between 2 to 365 days were recruited. The blood samples were collected for establishing age and sex-stratified reference intervals for FSH, LH, E2, To, DHEA-S and cortisol using Electrochemiluminescence, Cobas e 601 analyzer.
Results: The results are shown in table 1

	2-59 days n:345		60-179 days n:248		180-365 days n:100	
	Female	Male	Female	Male	Female	Male
	2.5th - 97.5th	2.5th - 97.5th	2.5th - 97.5th	2.5th - 97.5th	2.5th - 97.5th	2.5th - 97.5th
DHEA-S (ug/dL)	12.8 - 275.4	20.8 - 407.1	2.8 - 224.2	3.5 - 178.7	0.1 - 16.0	0.5 - 29.2
Cortisol (ug/dL)	0.5 - 23.0	0.6 - 19.6	0.2 - 23.4	1.0 - 26.0	1.2 - 23.9	0.9 - 23.4
To (ng/dL)	12.0 - 94.5	12.0 - 383.6	12.0 - 74.8	12.0 - 364.7	12.0 - 13.8	12.0 - 252.3
FSH (mIU/mL)	0.2 - 26.0	0.6 - 7.0	0.7 - 23.3	0.5 - 4.6	0.8 - 18.3	0.2 - 2.7
LH (mIU/mL)	0.1 - 3.5	0.4 - 10.1	0.1 - 3.1	0.2 - 7.6	0.1 - 0.9	0.1 - 3.0
E2 (pg/mL)	12.0 - 71.0	12.0 - 70.3	12.0 - 75.0	12.0 - 59.8	12.0 - 56.9	12.0 - 57.7

[Table 1: DHEA-S, Co, To, FSH, LH and E2 percentile]

Conclusions: This reference values specific for age and sex may help in this period of life to increase the diagnostic power of this parameters for the assessment of endocrine disorders.

P2-d1-623 Adrenals and HPA Axis 4

Highly elevated basal cortisol levels and their association with disease severity in critically ill paediatric patients

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Background: Enhanced activity of the hypothalamic-pituitary-adrenal axis during critical illness is considered to be a homeostatic adaptation that is essential for survival. However, in critically ill adults a highly elevated cortisol level was found to be an independent predictor of death.
Objective: To compare disease severity and mortality rates among critically ill children with and without highly elevated basal cortisol levels.
Methods: Medical records were reviewed of all children who underwent a Synacthen test in the paediatric intensive care unit in a tertiary medical center in 2002-2012. The tests were divided into two groups: Group I - highly elevated basal cortisol level (≥900 nmol/l) and Group II - below 900 nmol/l. Demographic and clinical data including age, gender, diagnosis, Glasgcow Coma Score (GCS) and Sequential Organ Failure Assessment (SOFA) score before the Synacthen test were obtained. Outcomes included duration of hospitalization, days of ventilation support, GCS and SOFA score at discharge and death.
Results: 81 Synacthen tests of 74 patients were analyzed. 60.5% of the patients were male; median age was 2 months (range 0-180 months) and median body weight 3.8kg (range 2.1-55 kg), with no statistically significant difference between the two groups in demographic characteristics. At presentation, Group I had lower mean GCS (6.3±4.7 vs. 10.1±4.5, p< 0.01) and higher mean SOFA score (10.7±4.7 vs. 8.1±4.0, p=0.08) compared to patients in Group II. Patients in Group I were ventilated during a larger part of their hospitalization (85.5%±31.9 vs. 62.5%±37.8, p=0.1). On discharge, mean GCS was lower (9.4±5.5 vs. 12±4.5, p=0.1) and mean SOFA score was higher (8.3±7.1 vs. 4.9±5.4, p=0.09) for Group I compared to Group II and mortality rate was twice (43.8% vs. 21.5%, p=0.07).
Conclusions: Very high basal cortisol levels in critically ill children were associated with greater illness severity and a higher mortality rate.

P2-d1-624 Adrenals and HPA Axis 4

Two novel mutations in CYP21A2 gene causing classic and non-classic congenital adrenal hyperplasia

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Background: Gene conversion events with the CYP21A1P pseudogene cause >95% of congenital adrenal hyperplasia (CAH). An amino acid sequence variant of uncertain significance in a patient with clinical diagnosis of CAH poses a diagnostic challenge.
Objective and hypotheses: We report two new mutations in CYP21A2 gene, one causing classic CAH and another causing non-classic CAH.
Methods: The mutant cDNAs were expressed in yeast and HEK-293 cells to assay 21-hydroxylase activity.
Results: Patient 1 was evaluated in childhood for genital ambiguity. She was diagnosed with simple-virilizing CAH based on elevated 17-hydroxyprogesterone (17OHP). Multiplex ligand-dependent probe amplification (MLPA) with mini-sequencing showed one variant pR483P. The other allele was deleted.
Patient 2 developed pubic hair at age of 9 years followed by a rapid progression of pubarche. When she was 9-9/12 years old, her bone age was advanced to 12.5 years. Cosyntropin stimulation test yielded a 17OHP level 36.9 nmol/L (1220 ng/dL). Genetic test identified a large deletion on one allele and a variant pV249A with "uncertain significance" on the other allele. The computer modeling predicted that this alteration might not be a disease-causing variation. The amino acid valine at position 249, however, is highly conserved, and another prediction algorithm suggested that this nucleotide change, g.1588T>C, might impair splicing.
The mutant cDNAs were expressed in yeast and HEK-293 cells to assay 21-hydroxylase activity. The conversion rates of 17OHP to 11-deoxycortisol were reduced to 12% and 0.5% of wild-type CYP21A2 for mutations V249A and R489P, respectively, in HEK-293 cells. In assays corrected for immunoreactive protein in yeast microsomes, Vmax was reduced to 32% and 14% of wild-type activities for mutations V249A and R489P, respectively, with Km values 0.7-2.4 μM.
Conclusions: The correlation of 21-hydroxylase activities with disease severity confirms that these are disease-causing mutations.

P2-d1-625 Adrenals and HPA Axis 4

Blood pressure, fludrocortisone dose and plasma renin activity in infants with classical adrenal hyperplasia due to 21-hydroxylase deficiency

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Background: Newborns and infants with salt-wasting congenital adrenal hyperplasia (CAH) require relatively high doses of fludrocortisone (FC) and may therefore be at risk for arterial hypertension.
Objective and hypotheses: To evaluate blood pressure, FC doses and plasma renin activity (PRA) in infants with CAH due to 21-hydroxylase deficiency.
Methods: 33 patients (18f/15m), who were diagnosed by newbornscreening, were prospectively followed until the age of 4 years. All patients were initially treated with both hydrocortisone (HC) and FC.
Results: From three to 18 months of age, mean daily FC dose was approximately 0.1±0.05 mg. At 24 months mean daily FC dose could be decreased to 0.05±0.02 mg.Initially, at three months of age, mean PRA was elevated (PRA 16.6±26.6 ng/ml/h) and normalized by the age of six months (PRA 5.3±13.1 ng/ml/h). The lowest mean PRA was measured at 24 months of age (PRA 1.8±2.7 ng/ml/h). Mean blood pressure was in the higher normal range at three and six months of age (RR systolic 100±25 mmHg and 105±21 mmHg, RR diastolic 66±19 mmHg and 68±16 mmHg). At twelve and at 18 months of age mean RR was highest and above the 95th centile (RR systolic 117±20 mmHg and 118±28 mmHg, RR diastolic 77±21 mmHg and 81±26 mmHg). At 36 and at 48 months RR was back to the mean initial RR levels (RR systolic 100±15 mmHg and 99±17 mmHg, RR diastolic 61±12 mmHg and 63±12 mmHg). Systolic and diastolic blood pressure correlated significantly with the administered fludrocortisone dose (r=0,3, p< 0.01).
Conclusions: Elevated RR was found at 12 and at 18 months of age in children with classical CAH under HC and FC treatment. Between 18 and 24 months of age mean FC dose could be decreased from 0.1 mg/day to 0.05 mg/day. The changing mineralocorticoid sensitivity in infants is a risk factor for the development of hypertension in patients with CAH, who are treated with FC. Therefore measurement of PRA or renin and blood pressure at regular intervals are essential.

P2-d1-626 Adrenals and HPA Axis 4

Assessment of adrenal function in patients with Prader-Willi syndrome

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Background: An annual death rate of the patients with Prader-Willi syndrome (PWS) is high (3%), and unexplained deaths have been reported in several patients with PWS. Central adrenal insufficiency (CAI) due to hypothalamic

dysfunction has been suggested as possible cause of deaths in PWS particularly in association with infection-related stress. Although several stimulation tests using insulin, methyrapone, low-dose or standard-dose ACTH have been carried out for patients with PWS, the results were controversial.
Objective and hypotheses: The aim of this study was to assess adrenal function in children and adolescents with PWS by insulin tolerance test (ITT).
Methods: We studied morning plasma ACTH and serum cortisol levels, and evaluated adrenal function by ITT in 36 Japanese patients with PWS (12 females and 24 males, aged 7 months-59 years). Of the 36 patients, 25 had deletions at 15q11-13, ten had maternal uniparental disomy of chromosome 15 (upd(15)mat) and one had epimutation.
Results: Basal levels of ACTH and cortisol were 12.9±8.0 pg/ml and 17.5±8.5 μg/dl, respectively. Five patients showed low levels of basal ACTH (< 5 pg/ml). In all patients, cortisol levels at 60 minutes after stimulation were within the reference range (> 20 μg/dl) with peak levels of 41.4±14.3 μg/dl. The average increase of cortisol from basal levels was 20.8±8.5 μg/dl. Most patients (26 of 36) showed peak cortisol levels at 120 minutes after stimulation.
Conclusions: These results suggest that basal and peak levels of cortisol are within the normal range in PWS patients, while peak responses of cortisol to insulin stimulation are delayed in most patients. Thus, it is likely that cryptic hypothalamic dysfunction alters secretion patterns of cortisol in PWS patients. Further studies are necessary to clarify the possible association between the altered response of cortisol to hypoglycemia and unexplained deaths in PWS.

P2-d1-627 Adrenals and HPA Axis 4

Normal ranges of basal and glucagon-stimulated free cortisol in children: a pilot study

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Background: Standard assays for serum cortisol measurements determine total cortisol (TC) concentrations but not the unbound biologically active serum free cortisol (sFC). Measurement of TC would be greatly influenced by alteration in cortisol-binding globulin (CBG) concentrations. It is, therefore, important to determine sFC levels when CBG levels are either decreased or increased.
Objective and hypotheses: To determine basal and glucagon-stimulated sFC in relation to TC, growth hormone (GH) and glucose levels in children.
Methods: Infants and children referred for glucagon test for evaluation of GH, were recruited. In this test baseline and stimulated serum GH, glucose and TC levels are routinely measured before and every 30 minutes for 180 minutes after IM administration of glucagon(30 mcg per kg, max of 1 mg). In addition sFC was taken at the same time points to all subjects. Serum GH and TC were determined by chemiluminescence. Serum FC was measured by chemiluminescence following equilibrium dialysis. Peak TC ≥ 20 mcg/dl was considered normal.
Results: Thirty-four subjects (15 girls, 19 boys) whose median age was 3.9 years (range, 1.3-13.8) were included. Mean baseline TC and sFC levels were 12.7 ± 5.8 mcg/dl and 0.49 ± 0.28 mcg/dl, respectively. Mean peak TC and sFC levels were 29.7 ± 9.6 mcg/dl and 1.5 ± 0.8 mcg/dl respectively. Baseline and peak TC and sFC levels were positively correlated
(r=0.78 $p< 0.001$ and r=0.91, $p< 0.001$, respectively). Compared to boys, girls TC and sFC were significantly higher at all times points (p=0.03 and p=0.04, respectively).
Conclusions: This pilot study suggests normal ranges for basal and glucagon-stimulated sFC for children. These normal ranges may be useful for the evaluation of the hypothalamic- pituitary-adrenal axis in children with CBG alterations.

P2-d1-628 Adrenals and HPA Axis 4

A large heterozygous deletion in the CYP21A2 gene in a girl with premature adrenarche and precocious puberty: divergence between genotype and phenotype and the diagnostic role of multiplex ligation-dependent probe amplification (MLPA) technology

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Introduction: Congenital adrenal hyperplasia (CAH) is a common autosomal recessive disorder . 21-hydroxylase deficiency accounts for about 90-95% of all CAH cases. Clinical features associated with CAH comprise a spectrum, ranging from salt wasting and simple virilizing forms, collectively referred to as classical 21-hydroxylase deficiency, to milder non-classical or late onset form (NCAH). Heterozygosity for CYP21A2 mutations in females could increase their risk of clinically manifesting hyperandrogenism.
Case study: We present a case of a 7-year-old female heterozygous for a mutation in CYP21A2 gene, referred to our Department for premature adrenarche and thelarche (pubertal stage PH2 B2), appeared at the age of 6 years, and advanced bone age (3 years). Clinical evaluation didn't show signs of virilization. Blood tests showed elevated basal 17-hydroxyprogesterone (4.5 ng/ml), pelvic and abdominal ultrasound excluded adrenal or ovary mass. Standard ACTH stimulation test showed an increase in 17OHP (11.4 ng/ml) compatible with NCAH. GnRH test confirmed gonadotropin-dependent precocious puberty. Direct gene sequencing didn't show mutation in the CYP21A2 gene while MLPA showed a heterozygous large deletion of exons 1,3,4,6,8.
Conclusions: Our findings bear out that there is an increased risk for symptoms of androgen excess in heterozygous carriers of mutations in CYP21A2 gene. In particular, large deletions in the CYP21A2 gene, as described in our case, could be responsible for particular and specific clinical and biochemical manifestations, resembling those of NCAH. In addition direct sequencing alone can be inadequate for the genetic definition of CAH. In fact, hemizygous or compound heterozygous subjects, that have a single peak of a wild or mutant allele in sequencing analysis respectively, could be carriers of large gene deletions, detected instead by MLPA analysis. Hence, we suggest the usefulness of MLPA analysis for rapid detection of deletions in the CAH.

P2-d1-629 Adrenals and HPA Axis 4

Adrenocortical tumors in childhood

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Background: Adrenocortical tumors (ACT) occur with a worldwide incidence of 0,2-0,3 cases per million. They account for 0,2% of all pediatric solid malignancies. Most of them are functional and the prognosis is related with the stage of the tumor at diagnosis.
Objective: To describe the presentation and evolution of three patients with ACT diagnosed between may 2011 and may 2012.
Case 1: An 11-years old girl who complained of acne and hirsutism. She had facial rounding with plethora, acne, hirsutism, central obesity, hypertension, Tanner B1, PH5 and clitoromegaly. An abdominal US showed a right adrenal mass of 160x150 mm with calcifications. Pulmonary and liver metastasis were found. A biopsy confirmed ACT. P53 marker was positive. She was treated with chemotherapy and died 5 months later.
Case 2: A 9-month-old girl was referred because of pubarque. She had PH Tanner 2 and clitoromegaly. An abdominal US revealed a left adrenal mass with calcifications of 47x32 mm. Workup showed hyperandrogenemia. The tumor was removed and ACT was diagnosed. P53 marker was positive. After 6 months free of illness hyperandrogenemia was found and a PET Scan revealed an abnormal image on the right adrenal. Complete excision of the lesion was made. To date the patient is free of illness.
Case 3: A 9-month-old girl was referred because of Cushing's syndrome. She had facial rounding, central obesity and height on the tirth percentile. The abdominal US showed an adrenal mass of 68 x 58 mm with calcifications. Lab workup showed hypercortisolism and hiperandrogenism. Surgery was per-

formed and ACT was confirmed. P53 marker was negative. After 3 months of controls her family decided to continue follow-up in another center.
Conclusions: Althought ACT are uncommon in childhood we diagnosed three cases in one year, after 10 years without seeing anyone. The analysis of P53 is useful as a sign of aggressive behavior and should lead to a more strict follow up.

P2-d1-630 Adrenals and HPA Axis 4

Age and gender affect cortisol levels to simplified low dose short synacthen test in children with asthma

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Background: Low dose short Synacthen test s(LDSST) are used widely in paediatric practice, however the intensity of sampling makes it technically challenging.
Objective and hypotheses:
(1) A simplified LDSST can be used to assess adrenal reserve in children without loss of sensitivity or specificity
(2) age and gender influence cortisol levels.
Methods: 269 subjects (160M), median age 10.0 years (range 5.1 - 15.2) were studied. Synacthen 500ng/1.73m^2 was administered intravenously at 09.00. Samples were collected at 0, 15, 25, 35 minutes, time points selected from raw data from children treated with ≥ 500mcg fluticasone daily, studied with more intensive sampling. (1)
Results: Peak cortisol was < 500nmol/L in 101/269 subjects (37.5%). 100 patients were treated with fluticasone ≥ 500mcg/day, of whom 43 subjects (43%) had peak cortisol levels < 500nmol/L, compared to 88 / 194 (45.5%) subjects from the reference data (p=0.142). Basal cortisol correlated with peak cortisol: r=0.55, (95% CI: 0.46, 0.63, p< 0.0001). Median basal cortisol increased by 10nmol/L per year of life, 95% CI = 6.54, 12.54, p< 0.0001. Time at which peak cortisol concentration was achieved was significantly related to the value of peak cortisol (p< 0.0001): Patients with the highest peak cortisol values had a later peak cortisol than those in whom cortisol levels were low. Peak cortisol decreased by 6.0nmol/L per year of life, 95% CI -10.9, -1.1, p=0.017, was 51.9nmol/L lower in boys than girls, 95% CI -84.81, -18.89, p = 0.002, and 96.8 nmol/L lower in those treated with oral corticosteroids, 95% CI -162.0, -31.6, p = 0.004.
Conclusions: A simplified LDSST can be used to study adrenal function during ICS therapy, without significant loss of sensitivity and specificity. Age and gender affect cortisol levels on the LDSST. This may reflect differences in susceptibility to adrenal suppression, or development changes in the adrenal axis.

P2-d2-631 Adrenals and HPA Axis 5

Cushing syndrome (CS) in children and adolescents: a retrospective review at presentation, diagnosis, management and outcome

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Background: CS is a rare but important condition in childhood, often associated with late diagnosis and significant long term morbidity.
Objective: To describe a tertiary centre's experience in the diagnosis and treatment of CS.
Population and methods: Records of all of the patients referred to this tertiary centre with a diagnosis of CS from 1983 until 2013 were reviewed.
Results: 30 patients (14 female) were identified. Median age at presentation was 8.9 years (range 0.2 - 15.5) and the delay between onset of symptoms and diagnosis was 1.0 year (range 0.04 - 6). Weight gain (23/30), hirsutism (17/30) and acne (15/30) were the most common presenting manifestations. Median BMI SDS at presentation was +2.27 (range -6.5 to +4.6); 15 patients had a BMI SDS > 2.0 while 3 patients presenting with hypertension had a BMI SDS < 0. Systolic hypertension was present in 8/30.
16 patients had a pituitary ACTH secreting adenoma, 11 primary adrenal disease, 2 ectopic ACTH secretion and in 1 case the aetiology remains unknown.

	Abnormal n (%)	Mean (SD)	Additional information
Urine Free Cortisol (nmol/24h)	17/18 (4)	3314 (7116)	
8am cortisol (nmol/L)	10/27 (37)	740 (557)	
8am cortisol (ng/l):			
- Pituitary tumours	7/13 (54)	48 (40)	
- Adrenal tumours	8/10 (80)	14 (21)	
- Ectopic ACTH	1/2 (50)	45 (8)	
Midnight cortisol (nmol/l)	27/27 (100)	661 (550)	
Midnight ACTH (ng/l):			
- Pituitary tumours	5/10 (50)	40 (26)	
- Adrenal tumours	6/7 (85)	22 (36)	
- Ectopic ACTH	2/2 (100)	66 (20)	
24h cortisol profile (mean value nmol/l)		555 (217)	
LDDS +48h (nmol/L) (20mcg/kg/day 6hrly)	20/20 (100)	620 (369)	Suppression means cortisol at +48h <50 nmol/l
HDDS +48h (80mcg/kg/day 6hrly)	Suppression		Suppression means cortisol at +48h <50% of basal value
- Pituitary tumours	9/10 (90)		
- Adrenal tumours	0/6 (100)		
- Ectopic ACTH	1/2 (50)		
CRH test	Rise ACTH or Cortisol		Response if: cortisol ↑ >20% ± ACTH ↑ >50%
- Pituitary tumours	8/9 (89)		
- Adrenal tumours	0/1 (0)		
- Ectopic tumour	1/2 (50)		

[Table 1 Investigations and their performance]

All of the patients underwent surgery. 8 patients received metyrapone but this was discontinued in 4 due to side effects. 20 patients remain in remission, 5 relapsed (1 deceased) and 5 were lost to follow up.
All patients required glucocorticoid replacement post-operatively but this was discontinued in 12 patients after a median duration of 1.1 years (range 0.5 - 2.1). Median BMI 2 years post treatment was 1.1 SDS (range -1.0 to +3.9).
Conclusions: A small number of hypertensive patients with CS present in an atypical fashion with a low BMI SDS. Although all patients will require glucocorticoid treatment, 50% of them will be able to discontinue it by 1 year.

P2-d2-632 Adrenals and HPA Axis 5

Double mutated allele [IVS2+5G>A; p.V281L] in non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency patients. Implications in genetic counseling

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Background: The most frequent CYP21A2 gene alteration described in non-classic (NC) form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21OHD CAH) is p.V281L missense mutation.
In our previous study (Marino et al Clin Endocrinol 2011), sequence analysis of three p.V281L-mutation patients in whom the phenotype was more severe than predicted by genotype (classic form) revealed an intronic alteration in the allele carrying the p.V281L mutation [IVS2+5G>A; p.V281L].
Objective and hypotheses: To determine the frequency of IVS2+5G>A intronic alteration in the alleles carrying the p.V281L mutation [IVS2+5G>A; p.V281L] in a group of 64 NC 21OHD patients with a genotype homozygous for p.V281L found by the 11-most-common-mutation screening.
Methods: Sequence analysis of 64 p.V281L homozygous NC 21OHD patients (128 p.V281L alleles).
Results: Sequence analysis revealed the presence of one double mutated allele [IVS2+5G>A; p.V281L], (1/128 alleles, frequency 0.78%). In addition, a 17 biallelic marker haplotype in intron 2 shared by all three [IVS2+5G>A; p.V281L] patients from the previous study was also found in this double mutated allele using haplotype analysis. The IVS2+5G>A mutation was on an HH1 background in the 4 cases, a frequency significantly higher than the one expected from the 10.37% HH1 frequency observed on 106 (102 control + 4 IVS2+5G>A) evaluated alleles (p= 0.0001 Fisher's exact test). Therefore, it could be speculated that the two mutations appeared together just once in an ancestral haplotype, suggesting a founder effect.
Conclusions: In our population the analysis to detect a second mutation in the p.V281L allele has significant implications for PCR-based detection in NC CAH patients, since incomplete genotyping could mistakenly identify these individuals as carriers of a milder affected allele, which would lead to wrong genetic counseling. In addition, this double mutated allele should also be assessed in other populations.

P2-d2-633 Adrenals and HPA Axis 5

The variability of mutations in patients with 21-hydroxylase deficiency in some ethnic populations resident in the Russian Federation

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Background: There are 3 phenotypical forms of CAH: salt-wasting (SW), simple-virilizing (SV), nonclassical (NC). Some prevalent allelic mutations were found to vary significantly in ethnic groups.
Objective and hypotheses: To investigate the spectrum of frequent CYP21 mutations in different ethnic groups in Russian population and to find between-group correlation.
Methods: 117 CAH patients from multi-ethnic populations in 4 regions of RF were analyzed (58 female/59 male): 37 from Udmurt Republic (UR), 24 from Dagestan Republic (DR), 19 from Perm Territory (PT), 37 from Bashkortostan Republic (BR). Ethnicity was identified by self-reported and analysis of their genealogy. The phenotypic form of CAH was based on clinical presentation and hormonal rates. The 70% had SW form,24,7% SV,5,3% NC. The 11 common mutations (del,I2spl,I172N, R356W, Q318X,V281L, P453S,P30L,V237E,G291S,L307insT) loci in the CYP21 were studied by allele-specific polymerase chain reaction (PCR).
Results: The 95,7% of alleles were characterized, in 4,3% we didn't find mutations. 70 were homozygous and 43 compound. The most frequent mutations were Del, I172N, I2spl, as in general population. The I2spl is prevalent in Udmurt, the R356W in Avar, Tatar and Bashkir, the I172N in Kumyk and Komi-Permyak, the I2spl and Del in Russian depends on region. There was no Del mutation in DR.

Allelic mutations	Frequency (%)								
Region	UR (n=62)		DR (n=44)		PT (n=31)	BR (n=60)			
Ethnicity/ Total %	Russian (R)(38)	Udmurt (U)(24)	Avar (A) (36)	Kymik (K) (8)	Komi-Permiak (K-P) (8)	Russian (R) (23)	Bashkir (B)(11)	Tatar (T) (27)	Russian (R) (32)
I2spl (30,2)	39,5	75,2	25	12,5	25	8,7	27,3	18,5	34,4
R356W (13,5)			38,8	25		8,7	36,3	29,6	
V281L (3,1)	2,6					8,7		11,2	
I172N (14,9)	26,3	4,1	11,1	50	75	17,4	9,1	7,4	
Del (23,4)	18,5	8,3				34,8		25,9	56,2
Q318X (12,1)	10,5	8,3	22,2			17,4	27,3	7,4	9,4
P30L (0,9)	2,6	4,2							

[CYP21 mutations in RF]

Conclusions: This study showed that CAH in some groups of the RF population have their own ethnic specific mutations.That can be useful for rapid genetic screening.

P2-d2-634 Adrenals and HPA Axis 5

Functional analysis of novel mutations inactivating the HSD3B2 gene

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Background: 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2) deficiency (3BHSD2D) is a rare cause of congenital adrenal hyperplasia. HSD3B2 deficiency manifests with a wide phenotypic spectrum including adrenal insufficiency, 46,XY disordered sexual development (DSD) and infertility.
Objective and hypotheses: To characterise HSD3B2 mutations found in patients with clinical symptoms indicative of 3BHSD2D.
Patients: Patient P1 and P2 presented with adrenal insufficiency and 46,XY DSD. Patient P3 manifested was a 46,XY baby born with ambiguous genitalia. No symptoms of adrenal insufficiency were noted in P3.
Methods: *HSD3B2* molecular genetic analysis was performed. Functional characterisation of HSD3B2 mutations was characterised in COS7 cells over-expressing wild-type (WT) or mutant HSD3B2, by measuring the conversion of pregnenolone, 17-hydroxypregnenolone or dehydroepiandrosterone to progesterone, 17-hydroxyprogesterone, and androstenedione respectively. In addition, cells were incubated with MG132, a protein degradation inhibitor, to investigate the effect of the mutations on protein stability. Expression of mutant and WT HSD3B2 was investigated by Western blot analysis.
Results: Patients with classic 3BHSD2D, P1 and P2, were homozygotes for the novel c.65insT and the severe T259M mutations, respectively. P3 was compound heterozygote for A82T and the novel Y339C mutations. Functional analyses revealed that c.65insT, T259M and Y339C completely abolished HSD2B2 enzyme activity, whilst A82T retained 4% of WT activity. Western blot analyses showed that all mutants compromised protein instability and MG132 treatment restored protein expression.
Conclusions: We describe three 3BHSD2D patients with a broad phenotypic expression, two with a classic phenotype and one with isolated 46,XY DSD.

Our data suggests a good genotype-phenotype correlation in 3BHSD2D patients. Importantly, 3BHSD2D should be considered in patients with isolated 46,XY DSD of unknown cause.

P2-d2-635 Adrenals and HPA Axis 5

Adrenal steroid determinations by ultra performance liquid chromatography tandem mass spectrometry in healthy newborn babies

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Background: The use of ultra-performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS) is increasing significance in clinical practice for determination of steroids. Advantages are the increased sensitivity, selectivity and reproducibility when compared with immunoassay techniques and the possibility of simultaneous measurement of different steroids on a small sample. Costs may decrease as this technology becomes more widely adopted.
Objective: To establish normal values of steroids: 17 hydroxyprogesterone (17-OHP), androstenedione (Δ4), dehydroepiandrosterone-sulphate (DHEAS), 11-deoxycortisol (S), cortisol (F), corticosterone and testosterone (T) by UPLC-MS/MS in term newborns (NB)
Patients: Blood samples of 128 (78 boys) NB, gestational age 39.1±1.3 weeks, with normal weigh (3421±458 g), vigorous apgar, 86(67%) born by cesarean delivery. Sampling was performed at discharge from the maternity (median 3, range 2-6 days). Hormonal dosages were correlated with age at the time of sampling, birth weight, percentage of weight loss, sex and gestational age.
Methods: UPLC-MS/MS coupled to quadrupole mass detector double tandem, Reagents: Perkin Elmer Kit Steroids®.
Results: 20 patients were excluded because of improperly submitted samples. The obtained values (ng/ml, median [range]) of steroids were: F 21.8 (2.4-147.4), corticosterone 1.1 (0.04-15.9), S 0.46 (0.08-1.7), DHEAS 464 (15-3121), 17OHP 0.3 (0-1.6), Δ4 0.27 (0.08-1.57) and T 0.27 (0.01-5.07). Boys had higher testosterone values (0.7 vs 0.08, p0.00) and Δ4 (0.4 vs 0.28, p0.007). There was only correlation between 17OHP and gestational age (r -0.30, p 0.02).There was no correlation between weight, gestational age, percentage of weight loss or age at the time of the sample and different steroids.
Conclusions: Normal values were defined by UPLC-MS/MS steroid measurements in healthy term infants in our population.

P2-d2-636 Adrenals and HPA Axis 5

Girls with precocious pubarche: lower SHBG levels at age 8 are followed by lower SHBG and higher C-reactive protein levels at age 22

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Background: Precocious pubarche (PP) in girls refers to the appearance of pubic hair before age 8 and is most commonly due to precocious adrenarche. Follow-up of PP girls into adolescence and adulthood has disclosed that a subset of girls with PP develop ovarian androgen excess and metabolic dysfunction. However, no prepubertal markers of an unfavourable outcome have so far been identified.
Objective: We aimed to test whether the circulating levels of SHBG track from childhood into adulthood and are then associated to measures of endocrine-metabolic health.
Study population: Girls with PP [N=30; age (mean ± SEM) 7.9 ± 0.3 yr at diagnosis and SHBG measurement] were reassessed at 21.8 ± 0.4 yr [body composition by absorptiometry, carotid intima-media thickness, circulating SHBG, androgens, glucose, insulin and C-Reactive Protein (CRP) in a fasting state within the follicular phase of the cycle]. Hormonal contraception was an exclusion criterion.
Results: Lower SHBG levels in childhood associated to lower SHBG (r= 0.56, p=0.001) and higher CRP levels (r= -0.48, p=0.007) in adulthood. In turn, lower SHBG levels in adulthood associated to higher levels of circulating insulin, androgens and CRP ($0.01 < p < 0.05$).
Conclusion: In PP girls, circulating levels of SHBG track from childhood into adulthood and are then associated to measures of endocrine-metabolic health. SHBG in childhood may contribute to identify PP girls who may benefit from early interventions aiming to improve the endocrine-metabolic state in adulthood.

P2-d2-637 Adrenals and HPA Axis 5

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency derived from novel compound heterozygous mutations (IVS2-13 A/C>G and p.E431K)

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Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is caused by mutations in the CYP21 gene encoding the steroid 21-hydroxylase enzyme, and has a broad spectrum of clinical forms, ranging from classical form to non-classical form (NCCAH). More than 90% of these mutations result from intergenic recombination between CYP21 and the closely linked CYP21P pseudogene. On the other hand, rare point mutations that arise independently of the pseudogene have been described to date.
Objective: We report a CAH patient, who showed atypical clinical form, and was eventually identified novel compound heterozygous mutations (IVS2-13 A/C>G and p.E431K).
Method and result: The patient was a 6-month-old Japanese boy, the first child of his parents. At 16 days old, he was referred to our hospital because of the elevated serum 17-OH-progesterone (17-OHP) levels (16.6 ng/ml) in neonatal screening. He didn't have significant physical findings (virilization, pigmentation, and salt-wasting), and his body weight gain was well. The findings of urine steroid hormone profile (pregnanetriolone: 3.632 mg/g cr, 11β-hydroxyandrosterone: 0.589 mg/g cr) at 28 days old stronglysuspected as 21-hydroxylase deficiency. As the compound heterozygous mutations (IVS2-13 A/C>G and p.E431K) in CYP21 gene were identified at 2 months old, we diagnosed as NCCAH. However, his body weight decreased, and his serum 17 OHP level elevated (99.5 ng/ml) at 3 months old. We started steroid replacement therapy. The steroid therapy improved his general condition, and normalized serum 17 OHP level.
Conclusions: IVS 2-13 A/C>G mutation is known as a common mutation for classical form of CAH and result in no CYP21 enzym activity. On the other hand, p.E431K is known as a rare point mutation. The residual enzyme activity is considered to result in the atypical clinical form on our case. Urine steroid hormone profile and gene analysis were important tools for a diagnosis on atypical CAH.

P2-d2-638 Adrenals and HPA Axis 5

Is maximal isometric grip force (MIGF) a potential long-term parameter to monitor metabolic control in children and adolescents with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH)?

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Objective: In CAH patients insufficient metabolic control caused by undertreatment leads to variable long episodes of hyperandrogenism, which are probably correlated with a higher muscle mass.
The hypothesis of this study was that CAH patients with poor metabolic con-

trol might have a higher MIGF due to higher androgen levels.
Design: We included 41 children with CAH, aged between 6.9 and 17.7 years (median 13.5, n=21 females) into this single-centre, cross-sectional, prospective, observational study. All patients had proven CAH (genetic groups: 0, n=14; A, n=16; B, n=9; D, n=2), received steroid substitution therapy. Determination of MIGF was done with a hand-held Jamar dynamometer. Sex-specific SDS values were calculated according to German references (Rauch et al. 2002).
Results (median, IQR: 25th;75th percentile)**:** MIGF SDS were elevated to 0.62 (right hand; 0,21, 1.52; p< 0.0001) and 0.68 (left hand; -0.30, 1.39; p< 0.0073). There was no difference of MIGF SDS between girls and boys. Correlation analyses showed a relation of MIGF with Δ bone age (=BA-CA): right: r_s=0.479, p=0.0064; left: r_s=0.447, p=0.0118. However, comparing MIGF values according to ΔBA (ΔBA < 1.0 a versus >1.0 a), we found a trend to higher values in children with advanced BA (right: 0.62 vs. 1.40, p=0.1265; left: 0.75 vs. 1.39, p=0.0773). In addition, there was a significant difference between children with low-normal 24h-urine pregnanetriol excretion (< 2000 µg/24h) vs. high pregnanetriol levels (>3000 µg/24h): 0.44, IQR -0.35, 0.81, vs. 1.11, IQR 0.01, 1.42; p< 0.05). Evaluation of other parameters (saliva 17OHP, serum T and 17OHP, BMI SDS, skinfold SDS, equivalent hydrocortisone and fludrocortisone dosage) showed no significant results.
Conclusions: MIGF is elevated in CAH patients. With respect to parameters of metabolic control in CAH patients (urine pregnanetriol, delta BA), our data show that MIGF measurements could be used as an additional parameter to monitor metabolic control.

P2-d2-639 Adrenals and HPA Axis 5

Utility of urinary steroid profiling to distinguish causes of urinary salt loss in infancy: evidence for adaptive response of steroid biosynthetic pathways and of characteristic presence of urinary cholesterol in secondary pseudohypoaldosteronism

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Background: Urinary salt loss in infants is a diagnostic challenge. Blood/urine analyses, renal tract imaging and genetic studies may all be needed. A urine GC-MS steroid profile (USP), on samples collected before confounding treatments are initiated, can differentiate all causes due to impaired aldosterone production or renal response.
These are deficiencies of cholesterol-pregnenolone conversion (C-P, P450scc; CYP11A1 and StAR protein), 3β(OH)steroid dehydrogenase (3β-HSD; HSD3β2), 21-hydroxylase (CYP21) and aldosterone synthase (CMOI/II;CYP11B2) as well as aldosterone resistance syndromes (pseudohypoaldosteronism, PHA) due to mineralocorticoid receptor or Na channel defects.
Objective and methods: To illustrate diagnostic USP features in these disorders with biochemical and molecular details of recent clinical cases, highlighting the following observations.
Results: USP distinguishes congenital adrenal hypoplasia (CAHypo/NROB1) and C-P defects from CYP21def . C-P defects and CAHypo both demonstrate reduced/absent steroid metabolites (metab.) but in CAHypo this is usually selective, notably 2 cases of NROB1 defects, showing only cortisol metab. 3βHSD shows reduced/absent cortisol metab. but this diagnosis requires demonstration of persistence of 3β(OH)-5-ene metab. beyond 3 months.
A previously reported feature of CAHypo is very low excretion of 3β(OH)-5-ene metab. characteristic in the first months of life. We now report very low 3β(OH)-5-ene metab. levels are also a feature common to CMOI/II and PHA, but not 3β-HSD or CYP21def. This may represent synthetic pathway adaptation to salt wasting (in a case of CMOI def. it was not seen on D1 of life, but evident by D8, when hyponatraemia had developed).
CMOI/II def. and PHA show increased corticosterone metab., with respectively reduced/absent or increased tetrahydroaldosterone. When PHA is secondary to UTI or anatomical defect, high urinary cholesterol is nearly always found, probably arising from tubular damage.

P2-d2-640 Adrenals and HPA Axis 5

Assessment of central adrenal insufficiency in children and adolescents with Prader-Willi syndrome

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Background: Recent studies revealed a central adrenal insufficiency (CAI) in 14-60% of Prader-Willi Syndrome (PWS) patients (pts) according to the used diagnostic method. CAI could be aggravated by rhGH recombinant human growth hormone (rhGH) treatment and may be a potential cause of sudden death in PWS pts.
Objective and hypotheses: Assessment of adrenal response in Low-Dose ACTH Test (LDAT) or/and in Glugacon Stimulation Test (GST) in pediatric PWS pts.
Methods: Eight pts with WPS, median age 11.6 years were included into the study. Five of them were treated with rhGH, median dose 0.21 mg/kg/week. LDAT with 1 µg tetracosactrin i.v. was made in 7 pts. Serum cortisol and ACTH at baseline and cortisol response 20, 30, and 60 min after stimulation were measured. GST with 0.1 mg/kg i.m. (top dose 1 mg) was made in 2 pts. Plasma cortisol at baseline, and 90, 120, 150, and 180 min after injection was measured. Both tests started at 8.00 a.m. A plasma cortisol response > 181.2 ng/ml (500 nmol/l) in LDAT and > 199.3 ng/ml (550 nmol/l) in GST was considered a normal response.
Results: Clinical characteristic of pts and data of hormonal tests are presented in Table 1.

pts	Age [year]	Height [SD]	Body mass/ height [%]	rhGH dose [mg/kg/w]	IGF-1 [ng/ml]	Basal ACTH [pg/ml] N 10-60	Basal Cortisol [ng/ml] N 50-230	Peak Cortisol [ng/ml]	test
1.♂	16.8	+0.6	128	0.21	821.3	33.7	81	204.1	LDAT
2.♂	11.5	+1.4	138	0.21	796.6	27.5	73.9	180.7	LDAT
3.♀	15.6	-1.9	116	0.21	261.8	24.4	54.8	163.7	LDAT
4.♀	13.5	-0.2	159	0.11	714.1	48.7	152.4	272.8	LDAT
5.♂	3.6	-0.2	133	0.21	325	45.5	94.3	187.9	LDAT
5.♂	4.2	-0.3	149	0.14	525.2	-	84.6	254.7	GST
6.♂	8.8	+1.9	102	0.09	393.6	55	48.8	204.1	LDAT
7.♂	16.9	-2.2	128	none	309	27.7	103.9	234.3	LDAT
8.♀	11.8	-1.1	248	none	163.4	24.9	54	233.9	GST

[Table 1]

On the base of LDAT test results CAI occurred in 2/8 pts (nr 2, and 3).
Conclusions: Our preliminary data confirm occurrence of CAI in WPS pts treated with rhGH (2/8). The study needs to be continued.

P2-d2-641 Adrenals and HPA Axis 5

Prevalence of late-onset congenital adrenal hyperplasia in Turkish children presenting with premature pubarche, hirsutism, or oligomenorrhoea

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Background: Late-onset congenital adrenal hyperplasia (LO-CAH), due to mutations in 21-hydroxylase, is a common autosomal recessive disorder. The clinical symptomatology may present at any age as premature pubarche (PP), cystic acne, hirsutism, polycystic ovarian syndrome (PCOS), and infertility.
Objective and hypotheses: Our aim was to determine the prevalence of LO-CAH presenting as PP, hirsutism, or PCOS, and to evaluate the molecular spectrum of CYP21A2 gene mutations.
Methods: A total of 126 patients (122 girls, 4 boys) with PP, hirsutism, or PCOS were included in this study. All patients underwent an ACTH stimu-

lation test. LO-CAH was defined by a stimulated 17-hydroxyprogesterone plasma level of > 10 ng/ml. Molecular analyses of the CYP21A2 gene were performed.
Results: Seventy-one of the 126 patients (56 %) presented with PP, 29 (23 %) with PCOS, and 26 (21 %) with hirsutism. Nine patients (7.1 %) were diagnosed with LO-CAH. The prevalence of LO-CAH was 8.4 % (n=6) in patients presenting with PP, 6.8 % (n=2) in patients with PCOS, and 3.8 % (n=1) in patients with hirsutism. Four different mutations (Q318X, P30L, V281L, and P453S heterozygosity) were found in six of nine patients (67 %) diagnosed with LO-CAH.

	Study Subjects Mean±SD	LO-CAH Mean±SD
Age(y)	10,4±3,8	9,8±3,7
BMI SDS	0,8±1	1±1,1
Height SDS	0,3±1	0,5±1
Bone Age SDS	1,1±1	2,1±0,4
T.Testosterone(ng/dl)	24±29	17±25
Cortisol peak(µg/dl)	29±6	32±5
17 OHP peak(ng/ml)	4,8±6	22±12
DHEA-S peak(µg/dl)	140±114	160±127
Androstenedion peak(ng/ml)	4±2	4±3

[Clinical characteristics and laboratory findings]

Conclusions: Late-onset congenital adrenal hyperplasia should be a differential diagnosis in patients presenting with PP, hirsutism, PCOS, and advanced bone age. Genetic analysis should be performed to confirm the diagnosis of LO-CAH.

P2-d2-642 Adrenals and HPA Axis 5

Prevalence and characterisation of testicular adrenal rest tumors in Chinese children and adolescent males with congenital adrenal hyperplasia

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Background: Testicular adrenal rest tumors (TART) was repoted as a common complication in adult congenital adrenal hyperplasia (CAH) patients. But the prevalence in Children and their characteristics had not been investigated fully, especially in China.
Objective and hypotheses: To summarize the prevalence, risk factors and characterization of TART in Chinese children and adolescent males with CAH due to 21-hydroxylase deficiency (21 OHD).
Methods: In the recent 4 years, there have been 44 males with CAH 21 OHD undergone testicular ultrasound scan in our clinic. We have diagnosed 13 cases of TART and summarized the characterizations.
Results: The prevalence of TART in our group was 29.5% with 11 salt wasters and 2 simple virilizers. The median age of TART diagnosis was 10.2 years. The median follow-up period of TART was 3.0 years. There were histories of CAH poor control before the diagnosis of TART in all of the 13 patients. We increased the doses of hydrocortisone in 5 cases of TART who refused operations or had small TART and led to tumor regression in two of those five patients. Testis-sparing surgeries were performed in eight patients and resulted in symptoms relieved. There were seven of those eight patients presented elevated FSH/ and LH after operations.
Conclusions: Prevalence of TART in our CAH 21OHD children and adolescent males was 29.5%. Testicular ultrasound was useful in TART screening. Doctors should think about TART in CAH 21OHD patients with poor control, especially in post-pubertal patients. Delay management of TART might lead to impaired testicular function. Increased doses of glucocorticoid might be effective in TART of small size. Testis-sparing surgery should be considered if necessary.

P2-d3-643 Adrenals and HPA Axis 6

Prevalence and long-term follow-up outcomes of testicular adrenal rest tumors in children and adolescent males with congenital adrenal hyperplasia

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Background: There are a few studies regarding the prevalence of testicular adrenal rest tumors (TARTs) in boys and adolescent males with congenital adrenal hyperplasia (CAH), and there is little information regarding the treatment outcomes in patients with TARTs.
Objective and hypotheses: The aim of this study was to determine the long-term treatment outcomes in boys and adolescent males with CAH.
Methods: Sixty boys and adolescent males with CAH, who were between 2-18 years of age, were included in the study. Fifty-five patients had 21-hydroxylase deficiency (21-OHD) and 5 patients had 11-β hydroxylase deficiency (11β-OHD). All patients were screened for TARTs by scrotal ultrasonography (US) performed by an experienced radiologist.
Results: TART prevalence was 18.3% in 2-18 years' of age; 8 patients had 21-OHD, and 3 had 11β-OHD. The youngest TART patient was 4 years old, whereas 8 patients RTs were at puberty. Only 2 patients had tight metabolic control: 8 patients had stage 2, 1 had stage 4, and 2 had stage 5 rest tumors. In 4 patients with stage 2 TARTs, tumors disappeared after high-dose steroid treatment and did not recur. Shrinkage of tumor was observed in 2 patients. Testis-sparing surgery was performed in 1 patient with stage 5 tumor. Gonadal functions were normal in patients with partially regressed tumors. Two patients became fathers of healthy male off-springs.
Conclusions: Detection and treatment of TARTs in children with CAH at younger ages, earlier stages, may prevent infertility in adulthood. Therefore, we recommend that scrotal US screening should be performed in every 1-2 years starting from early childhood.should be performed in every 1-2 years starting from early childhood.

P2-d3-644 Adrenals and HPA Axis 6

The 17α-hydroxyprogesterone (17 OHP) neonatal screening in Bulgaria 2010-2012

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Background: One strategy for reducing the number of undiagnosed patients with congenital adrenal hyperplasia (CAH) has been the introduction of newborn screening (NS) programs. The measurement of 17 OHP in dried blood spots worldwide showed its effectiveness in the early recognition of CAH due to classic 21 hydroxylase deficiency, thus preventing life-threatening salt losing crisis and incorrect gender assignment. Data on CAH incidence in Bulgaria before the implementation of 17OHP-NS were lacking.
Objective and hypotheses: Analysis of the NS CAH data after its nationwide implementation in 2010.
Methods: The 17 OHP (Delfia®) NS was introduced after a pilot study 2002/03 by using the existing (since 1978) screening logistic. Cut offs: 30 nmol/l (term newborns, 3-4th day of life) until the end of 2010, then adoption of ISNS referent values; screened population 148 955 newborns (coverage 78% for the whole period). Some of the samples were analysed retrospectively.
Results: Elevated 17 OHP were found in the 1st screening card in 953 (RR1= 0.64%) newborns. Further stratification in high and low risk groups with subsequent follow up (RR2=0.18%) and confirmation of the pathological screening results led to the diagnosis "classical CAH" in 16 newborns (8 boys, 8 girls), average age at screening 3,8±1,6 (median 3) d, at therapy start 16,4 ±6.6 (median13) d; Incidence 1:9310 screened newborns (10.7/100 000).
Conclusions: 17OHP- NS seems to be a complicated but successful tool for early diagnosis of CAH. A targetted and permanent education program of medical professionals and parents is needed for improving age at therapy

start. Further delineation of the molecular genetic background will facilitate diagnosis and treatment in newborns with suspected CAH from the 17 OHP screen.

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P2-d3-645 Adrenals and HPA Axis 6

Cushing disease in paediatric population: diagnostic and therapeutic difficulties

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Background: Cushing disease in paediatric versus adult population is very rare and its diagnostics can be a challenge.
Objective and hypotheses: The aim of the study was clinical, endocrinological and radiological assessment, analysis of treatment efficacy and recurrence during a long term follow-up in paediatric patients with Cushing disease.
Methods: We analysed 23 patients (11 girls, 12 boys) treated in our centre since 1994 to 2012. Age at the diagnosis was 5-17 yrs, mean 14 yrs. Short stature was present in 50% of patients, but all children presented with a decreased growth velocity. Obesity was observed in 82%, mean BMI 24,7.
Results: ACTH levels were 536 to 15pg/ml, mean 115pg/ml, in 30% ACTH level was within the normal range (N 10-60pg/ml). Cortisol level at night (24:00) was 8,2-52,1µg/dl, mean 24,5µg/dl. CRH test was performed in 18 patients, ACTH level increased above 35% in 66% of patients, cortisol level increased above 14µg/dl in 77%. In one patient cortisol suppression was observed already after low dose of Dexametasone, the rest presented cortisol suppression after high dose of Dexametasone. Pituitary adenoma was apparent in MRI in 40%, in the rest the lesion was not seen. Bilateral inferior petrosal sinus sampling (BIPSS) was performed in 11 patients, in all the pituitary ACTH excess was confirmed. The initial treatment in all patients was neurosurgery, with 82% efficacy. 4 patients needed resurgery, in 2 radiotherapy was performed after not-successful resurgery. Recurrence was observed in 3 patients after 1, 5 and 8 years of follow-up.
Conclusions: The most characteristic symptom of Cushing disease that was presented in 100% of paediatric patients was decreased growth velocity. In the case of incoherent results of the endocrinological and radiological examinations the BIPSS has a great diagnostic value. Patients should be closely followed-up due to the possibility of recurrence after many years since the initial treatment.

P2-d3-646 Adrenals and HPA Axis 6

Reduced uterus body length in girls with congenital adrenal hyperplasia (CAH)

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Background: The reduced uterine size and delay of puberty were described in girls with CAH. This is explained by disbalance between estrogens and androgens due to inadequate control of disease in pre- and pubertal patients. It's possible that not only compensation, but prenatal androgen excess may affect development of uterus.
Objective and hypotheses: To estimate the uterus body length depending on the compensation of CAH
Methods: The study included 37 girls with classical form of CAH (17 - salt-wasting (SW), 20 - simple virilizing (SV). Average age was 15.5±1.78 years, Tanner 3-5, bone age 16.9±1.6 years. Patients were divided into 2 groups: group 1 - well compensation and subcompensation for a long time (n=23), group 2 - inadequate compensation with symptoms of severe hyperandrogenia (n=14, SV-10, SW-4, among them 9 girls, who began receiving steroid substitution therapy after 3 years of age (3-13) and 5 girls received steroids irregularly). Serum estradiol were measured by chemiluminescent method, 17-OH-progesterone (17-OHP) by RIA. Uterus body length was determined by transabdominal ultrasonography.
Results: Mean uterus body length in total group (n=37) was 4.01±0.46 cm, which corresponds to lower limit of reference range (4-5 cm for 14-16 years, Dobrolovich, 2011). The time of menarche in menstruating patients (n=31) was normal (13.3±1.6), 6 girls had primary amenorrhea (all were decompensated). Negative correlation was observed between uterus body length and serum 17-OHP (r_s= -0.4, P = 0.012), while no significant correlation was observed between uterus body length and serum estradiol (r_s= 0.3, P = 0.07). There were no significant differences in uterus body length between compensated and decompensated patients (4.09±0.48 vs 3.88±0.37, respectively, P>0.05).
Conclusions: According to our data reduced length of uterine body is observed in most of adolescent girls with classical form of CAH, independently of the degree of compensation.

P2-d3-647 Adrenals and HPA Axis 6

Final height in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency treated with glucocorticoids: factors influencing the outcome

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Background: Patients with Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency are at risk for decreased final height. One of the most important therapeutic goals is the maintenance of normal growth.
Objective and hypotheses: The aim of the study was to evaluate factors influencing final height in CAH patients, analyzing the growth velocity in different phases of development (infancy, childhood, puberty).
Methods: 56 adult patients (30 females and 26 males) with CAH treated with glucocorticoids were retrospectively examined. The SD score for final height (FH SDS) and corrected height (FH-TH SDS, defined as final height SDS - target height SDS) were determined. Growth pattern, mean daily hydrocortisone dose and hormonal control were collected.
Results: FH SDS was reduced in all patients (males:-1.7±1; females:-1.07±1.35). FH-TH SDS was -1.24±1 in males and -0.45±1.13 in females. There was a significant decrease in growth velocity during infancy and puberty; the dose of steroids taken in these phases was inversely correlated to FH (FH and cortisol dose at infancy: r=-0.41, p=0.01; FH and cortisol dose at puberty: r= -0.38, p=0.003). Pubertal growth correlated negatively with steroid dose given during puberty (r_s= -0.54, p< 0.001). FH and pubertal growth were significantly reduced in patients treated with more than 17 mg/mq/die of hydrocortisone at the start of puberty, if compared with patients treated with lower doses (p< 0.001). The degree of hormonal control, BMI in childhood and puberty, the age of diagnosis and the clinical form did not correlate with FH.
Conclusions: Patients with CAH do not achieve an adequate final height with conventional therapy. Growth during infancy and puberty is sensitive to excess of glucocorticoids: a careful management of the therapeutic dose is necessary to improve height outcome, in particularly doses of glucocorticoid should not exceed 17 mg/mq/die during puberty.

P2-d3-648 Adrenals and HPA Axis 6

Management of Cushing disease in children and adolescents after first line treatment failure: report of a single centre experience

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Background: Cushing disease (CD) is rare in children and adolescents. First line treatment is selective adenectomy via transsphenoidal surgery (TSS). Disease relapse can occur unpredictably after TSS and can be difficult to treat with effective and safe second line therapies.

Objective and hypotheses: The aim of this study is to report the outcome of CD in a series of children and adolescents treated in our Centre in the last 20 years.
Methods: Eleven patients (pts), 9 males, were diagnosed in our centre with CD at 14 ±2.8 years, between 1991 and 2011. All cases underwent TSS (by the same surgeon) as 1st treatment.
Results: Overall after 1st TSS 6 pts were not cured or relapsed (3 pts). 2nd line treatments were:
a) TSS in 4 pts when pituitary adenoma was localized,
b) gamma knife radiosurgery (γ-k) in 1 pt after 2nd TSS failure and in another case with parasellar adenoma
c) medical treatment (ketoconazole, pasireotide) when 2nd TSS failed and γ-k was not feasible,
d) adrenalectomy in one pt upon family request (after ketoconazole trial).
2nd TSS was ineffective in 2/4 pts that subsequently underwent γ-k or medical treatment (pasireotide); out of 2 γ-k treated pts, 1 was cured, the other showed partial clinical improvement.5/6 pts are in remission at last control: 3/6 needed more than 2 treatments, the adrenalectomized pt developed Nelson's syndrome and needed more than one TSS. The cure rate after 1st TSS is 54.5 %, and at last control is 91% with median follow up free of CD of 10.9 yrs (0.9-21.5). The favorite 2nd line treatments were TSS and γ-k surgery, with successful results in 50% of pts. Adrenalectomy was the last chance therapy, and caused severe Nelson's syndrome.
Conclusions: Our study shows the difficulty of management of unsuccessful 1st line treatment of CD; the choice of the 2nd line therapies depended on localization of pituitary adenoma, severity of CD, previous treatment failures and available new medical therapies.

P2-d3-649 Adrenals and HPA Axis 6

Non-classical CAH: molecular evaluation of 287 subjects from Northern and Southern Italy with comparison between genetic and hormonal results

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Background: Non classical congenital adrenal hyperplasia (NC-CAH) due to 21-hydroxylase deficiency (21OHD) is one of the most common inherited defects of steroidogenesis. It is caused by mutations in the *CYP21A2* gene that can be grouped in three categories according to the predicted level of enzymatic activity:
A (complete loss of activity),
B (severe) and
C (mild).
Objective and hypotheses: The genetic characterization of suspected NC-CAH subjects with stimulated 17OHP values ranging from 800 and 15.000 ng/dl in order to: investigate the genotype and the contribution of the 1st and 2nd allele on the 17OHP levels; review the pathologic hormonal levels.
Methods: 287 subjects were investigated by complete sequencing of the *CYP21A2* gene and by MLPA using the MRC-Holland P050B2 kit in order to identify all possible mutations including variation of the copy number.
Results: The 71.8% of the subjects showed both the alleles affected (37.4 % are compound heterozygous C/C, the 15.5 % are C/B and the 43.7 % are C/A), the 21.2 % resulted heterozygous and 7% normal. Among the group C/C the 50.6 % of the subjects are homozygous for V281L mutation.Taking into account the different mutations present in the 1st allele we found that the levels of 17OHP both basally and stimulated were progressively and significantly higher than the other group when the characterizing mutations were P482S, 3'UTR 13 G>A, P453S, V281L or P30L, respectively. Also the 2nd allele showed an influence on basal and stimulated 17OHP if the 1st allele is setted (i.e. V281L mutation). The V281L mutation is more frequent in the South Italian patients, instead the 3'UTR *13 G>A and the genic deletion are more frequent in North Italian patients.
Conclusions: Among affected subjects, the 94% showed 17OHP stimulated values >2000 ng/dl and only 1% values < 1000 ng/dl.

P2-d3-650 Adrenals and HPA Axis 6

Puberty is critical for the development of bone mineral density impairment and increasing fat mass in patients with congenital adrenal hyperplasia

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Background: Patients with congenital adrenal hyperplasia (CAH) receive glucocorticoids as replacement therapy. Glucocorticoid therapy is the most frequent cause of drug-induced osteoporosis.
Objective and hypotheses: The objective of the current study was to describe bone mineral status and body composition in prepubertal CAH patients, and the evolution through puberty.
Methods: We enrolled 29 prepubertal children with the classical form of CAH (16 girls and 13 boys), aged 4.8 to 11.5 years at baseline. All patients were receiving cortisone as replacement therapy. We assessed fat mass (FM), free fat mass (FFM) and BMD by dual-energy x-ray absorptiometry at the lumbar spine and the whole skeleton at enrollment, and after completion of the pubertal period. We compared BMD, FM and FFM values of CAH patients with those of 116 healthy controls of comparable ages.
Results: At baseline lumbar spine BMD values of CAH patients (0.755±0.112 g/cm^2) were not different from those of healthy controls. Similarly, whole body BMD measurements (0.902±0.139 g/cm^2) did not differ from those of healthy subjects. After puberty we observed significantly lower BMD values of CAH patients both at the lumbar spine (1.162±0.133 g/cm^2, $P< 0.05$), and in the whole skeleton (0.161±0.098, $P< 0.05$).
When BMD data were expressed as z-scores, we could observe a mean decrement after puberty of -0.2 (1.1) in the lumbar spine, and of -0.7 (1.1) in the whole skeleton.The mean decrement in BMD z-score of male patients was significantly larger than that of female patients in both skeletal sites. Fat mass and fat body percentage were significantly higher in adult patients, compared with controls in both sexes.
Conclusions: Our data identify the pubertal period as the one critical for the development of bone density impairment and **increasing fat mass** in CAH patients. It is therefore important to monitor closely the bone mass acquisition in relation to the replacement therapy during puberty in CAH patients.

P2-d3-651 Adrenals and HPA Axis 6

Congenital generalised hypertrichosis terminalis with gingival hyperplasia

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Introduction: Congenital generalized hypertrichosis terminalis (CGHT) is a rare condition characterized by excessive growth of pigmented terminal hairs and often accompanied with gingival hyperplasia.
Case study: We report a 4-year old boy, from normal pregnancy, who presented at our department at the age of four months with excessive growth of hair from birth, overweight, high blood pressure. Prenatally by ultrasound examination was diagnosed congenital hydronephrosis of the right kidney. There was no consanguinity. On examination he had distinct facial features, abundant facial hair and profuse hair on upper, lower limbs and on the back. Laboratory tests and imaging studies do not proved androgen producing tumor (ectopic or from adrenal glands) or Cushing syndrome. We considered syndromes with CGHT including Barber Say syndrome. The karyotype 45, XY, der (13;14)(q10;q10)could not explain the phenotype of the child.
At the age of 8 months, after several urinary infections, he underwent right nephrectomy.
During the second admission to the department, at the age of 4 years, clinical examination showed normal intellectual development, generalized hypertrichosis and gingival hyperplasia. Laboratory exams showed normal function of the single kidney, no hormonal disturbance; heterozygous deletion on 17 q 12 was discovered.

Conclusion: Although benign in their clinical course, syndromes with CGHT may include other disorders (as in our patient) and as well may result in cosmetic disfigurement and psychological trauma for patients and their families.

P2-d3-652 Adrenals and HPA Axis 6

Pelvic ultrasound findings in prepubertal girls with precocious adrenarche born appropriate for gestational age with evidence of metabolic correlates of PCOS

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Background: Precocious adrenarche (PA) refers to the onset of clinical findings of androgen excess in girls under 8 years of age. It has been associated with an increased risk of functional ovarian hyperandrogenism after puberty, and a connection between PA and polycystic ovary syndrome (PCOS) has been suggested.
Objective and hypotheses: To compare pelvic ultrasound findings of girls with PA born appropriate for gestational age (AGA) with body mass index (BMI) matched healthy peers, and to investigate whether the ultrasound findings in AGA born PA girls are associated with PCOS antecedents.
Methods: We conducted a cross-sectional study on 56 AGA born girls with PA (mean ±S.D.) age 6.9 ±0.6 years) and 33 BMI -matched prepubertal peers born AGA (mean ±S.D.) 7.1 ±1 years). Hormonal data, standard 2-h oral glucose tolerance test derived Insulin sensitivity (IS) index (ISIcomp), homeostasis model assessment of IR (HOMA-IR) indices and pelvic ultrasound findings were compared. Correlations of pelvic USG findings with clinical and metabolic data were investigated.
Results: PA girls had higher uterine length (UL) (p=0.01) and UL SDS (p=0.02) than BMI- matched peers. Mean ovarian volume (MOV), MOV SDS, uterine volume, uterine cross-sectional areas and ovarian morphology (homogeneous, paucicystic or multicystic) were similar between the groups (p>0.05). MOV and MOV SDS correlated significantly with ISI_{comp} (r= -0.683, p< 0.001; r= -0.760, p < 0.001; respectively). Correlations of pelvis USG findings with other biochemical data failed to reach significance (p >0.05). Multivariate regression analysis revealed that ISI_{comp} had the most significant effect on MOV SDS (R^2=0.731, β= - 4.784, p=0.001).
Conclusions: AGA born PA girls have higher UL measurements than AGA born BMI-matched peers. In AGA born girls with PA, decrease in IS may be the main trigger in the sequence of events leading to PCOS.

P2-d3-653 Adrenals and HPA Axis 6

Late-onset congenital adrenal hyperplasia: new treatment strategy with sub-physiological dose dexamethasone preserves endogenous cortisol stress-response

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Background: Late-onset congenital adrenal hyperplasia (CAH) is characterized by sufficient cortisol and aldosterone production at the cost of androgen overproduction. Hydrocortisone or dexamethasone in (supra) physiological doses aiming at normalising androgen levels are current treatment options. The downside is suppression of endogenous cortisol production resulting in corticosteroid dependency.
Objective and hypotheses: To treat children with late-onset CAH with a sub-physiological dose of 0.025mg dexamethasone in order to normalize androgen levels, without a detrimental effect on endogenous cortisol production.
Methods: 5 patients diagnosed with late-onset CAH on the basis of clinical presentation, biochemical analyses and genetic testing were treated with dexamethasone. Anthropometric and biochemical measurements, and bone age were determined on a regular base. During treatment, an ACTH test was performed to measure maximum cortisol response. Outcome parameters were normalisation of androgens and deceleration of progression of bone age with sufficient endogenous cortisol response.
Results: Androgen levels normalized in all patients resulting in a deceleration of advancement of bone age, without detrimental effects on endogenous cortisol production. One patient needed hydrocortisone stress dosing only.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Male	Female	Female	Male
Age at start treatment (years)	9.9	8.1	8.3	7.9	10.8
Target Height (SDS)	+0.1	-0.5	-0.3	-1.1	0
Height at start of treatment (SDS)	0	+1.0	-0.2	-0.6	-0.4
Height at end of follow-up (SDS)	-0.7	+0.6	-0.5	-0.6	-0.2
Duration of follow-up (years)	3.7	2.8	1.2	1	4
BA-CA at start of treatment (years)	+1.5	+3.8	+2.1	+2	+3.5
BA-CA at start of follow-up (years)	0	+1	+1	+1	0
Stimulated cortisol (nmol/l)	356	720	555	524	579

[Table]

Conclusions: Late-onset CAH treatment with subphysiological dexamethasone seems to be a promising novel treatment strategy in late-onset CAH patients. The advantage of this treatment strategy compared to current strategy is that the adverse effects of hyperandrogenism can be reversed while preserving the endogenous cortisol stress-response.

P2-d3-654 Adrenals and HPA Axis 6

Clinical characteristics and genetic analysis of patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED) - single center experience during 44 years (1968-2012)

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Background: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autosomal recessive disorder. The classic triad includes chronic mucocutaneous candidiasis, hypoparathyroidism and Addison's disease. APECED is associated with mutations of a single gene, designated autoimmune regulator (*AIRE)*. To date, more than 60 different mutations of the AIRE gene have been described. Studies conducted so far have not established significant genotype-phenotype relationship.
Methods: Clinical data were collected in a retrospective way from medical records of all patients with APECED syndrome treated in Institute for Mother and Child Health Care of Serbia, for the period 1968-2012.
Results: Fourteen APECED patients (6 boys) from 13 unrelated families were identified and included to the study. In our group, presentation of the disease was 7.4 years (range 1-17). Hypoparathyroidism and Addison's disease revealed in 13 children median age 9.8 (range 5-17) and 11 years (range 4-20). Chronic mucocutaneous candidiasis was established in 10 patiens aged 8.2 years (range 1-17). Other related disorders were: alopecia in 6 patients; pernicious anemia, malapsorption and gonadala failure in three patients; vitiligo, ceratoconjuctivitis, autoimmune hepatitis and ectotermal dystrophy in one patient. Molecular analysis was performed in seven patients and revealed that all are compound heterozygotes for two mutations of the *AIRE* gene, two were novel and so far not reported
Conclusions: APECED syndrome is a rare condition. However, it should be taken into consideration in every child with chronic mucocutaneous candidiasis, hypoparathyroidism and Addison's disease. *AIRE* gene mutation detection is a reliable tool in diagnostics of APECED syndrome, especially in patients with atypical presentation. Regular follow up of adrenal function in needed, in order to prevent adrenal crisis and start substitution therapy, as soon as adrenal insufficiency in noted.

P2-d1-655 Adrenals and HPA Axis 7

Carrier status for 21-hydroxylase deficiency can be a factor in the variable phenotype of hyperandrogenism

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Background: Congenital adrenal hyperplasia (CAH) is a common autosomal recessive disorder primarily caused by mutations in the CYP21A2 gene. Heterozygosity for CYP21A2 mutations in females increases their risk of clinically manifesting hyperandrogenism.
Objective and hypotheses: To characterize the mutations in the CYP21A2 gene on symptomatic female carriers and associate the genotype to their symptoms.
Methods: The study population consisted of 19 girls with premature adrenarche, 17 adolescent females and 30 women with clinical signs of hyperandrogenemia. Direct DNA sequencing and multiplex ligation-dependent probe amplification (MLPA) analysis were used to identify mutations in the CYP21A2 gene.
Results: Most frequent mutations among the carriers were the mild c.1683G>T (p.Val281Leu) (53.0%), followed by c.1994C>T (p.Qln318stop) (18.2%), c.2665C>T (p.Pro482Ser) (10.6%), c.1752G>A p.Val304Met (6.1%), c.2578C>T (p.Pro453Ser) (6.1%), (1.5%), c.2296G>A (p.Ala391Thr), large deletion/conversion exons 1-4 (1.5%), large deletion/conversion exons 6-8 and c.707_714delGAGACTAC (8bpdelE3) (1.5%). Higher values of stimulated 17- hydroxyprogesterone (17-OHP) levels were found in the carriers of the c.1683G>T (p.Val281Leu) mutation compared with carriers of other mutations (mean = 24.7 nmol/L vs 15.6 nmol/L).
Conclusions: Females with increased risk of hyperandrogenism are likely to bear heterozygous CYP21A2 mutations and the risk to a certain extend can be related to their genotype. Therefore, a systematic evaluation of 17-OHP values in combination with the molecular testing of CYP21A2 gene.

P2-d1-656 Adrenals and HPA Axis 7

Reproducibility and utility of an overnight 0.25 mg dexamethasone suppression test as a marker for corticosteroid sensitivity in children with asthma

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Background: Inhalation corticosteroids (ICS) are the cornerstone of long-term asthma control in children. However, there is considerable inter-individual variation in sensitivity to corticosteroids, leading to over- as well as undertreatment. A simple and fast test to predict corticosteroid sensitivity could help to provide a more tailored therapy to children with asthma.
Objective and hypotheses: To study the reproducibility and utility of an overnight 0.25 mg dexamethasone suppression test with post-dex salivary cortisol levels as a marker for corticosteroid sensitivity in asthmatic children.
Methods: 23 children with atopic asthma were recruited to undergo two overnight 0.25 mg dexamethasone suppression tests with an interval of 1 month. Salivary cortisol levels were measured before and after ingestion of dexamethasone.
Results: Cortisol levels before dexamethasone correlated well between test 1 and 2 (r = 0.56; p=0.026). However, cortisol levels, change in cortisol levels or percent change in cortisol levels after dexamethasone did not correlate between the two tests (r = 0.34; p=0.20; r = 0.31; p=0.25 and r =0.29; p=0.28 respectively). ICS dose per kg did not correlate with baseline cortisol levels or cortisol levels, change in cortisol levels and percent change in cortisol levels after dexamethasone. Height SDS and BMI SDS did not correlate with ICS dose per kg, baseline cortisol levels, and cortisol levels, change in cortisol levels or percent change in cortisol levels after dexamethasone.
Conclusions: An overnight 0.25 mg dexamethasone suppression test in children with asthma shows poor reproducibility regarding salivary cortisol levels after dexamethasone. In addition, the 0.25 mg dexamethasone suppression test, in its present form, is not suitable for clinical practice in children with asthma to predict corticosteroid sensitivity.

P2-d1-657 Adrenals and HPA Axis 7

Cheilognathopalatoschisis and cognitive disturbances after prenatal dexamethasone treatment in a girl with congenital adrenal hyperplasia (CAH)

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Introduction: Prenatal treatment of classic CAH with dexamethasone (DXM) to prevent or reduce virilisation in affected females has been described as an effective modality to suppress fetal androgen production and consequently to prevent virilisation of affected girls and to reduce female reconstructive surgery. However, limited data are available concerning the adverse events in the mother and the neonate. Therefore, the Endocrine Society regarded this treatment as experimental.
We describe a girl with classic CAH and cheilognathoplatatoschizis and cognitive disturbances after her mother was treated with DXM during pregnancy.
Case presentation: The girl was the fourth child of healthy parents. Her older sister, was born with severe viralisation of the external genitalia (Prader 4) and was diagnosed with classic salt wasting CAH due to a 21-hydroxylase deficiency. Both parents were carriers of a classic mutation in the CYP21A2 gene. During this pregnancy, the mother started with oral dexamethason 0,5 mg three times per day from the 6th week of pregnancy. Fetal sex determination in maternal blood and mutation analysis of the CYP21A2 gene in chorion villus biopsy revealed an affected girl. Therefore, DXM treatment was continued during the whole pregnancy.
The girl was born at 36 weeks gestational age with slightly virilised external genitalia (prader 2) and a bilateral cheilognathopalatoschizis that had to be corrected surgically in several tempi.
At the age of 6 years, she underwent psychological testing because of learning difficulties revealing weak memory and a dysharmonic profile between verbal and performance scores.
Conclusion: The potential hazards of DXM treatment during pregnancy for mother and child have not been well investigated so far, and there are concerns about physical and psychological consequences. Our case report stresses the urgent need for follow-up data on this treatment regime.

P2-d1-658 Adrenals and HPA Axis 7

Testicular adrenal rest tumors in children with congenital adrenal hyperplasia

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Background: Testicular adrenal rest tumors (TART) are an important cause of infertility in male patients with congenital adrenal hyperplasia (CAH). It may occur in childhood and lead to irreversible lesion of testis.
Objective: The aim of our study is to estimate the incidence, clinical and ultrasound features of TART in male patients with CAH.
Methods: We studied 42 boys, aged from 0.5 to 18 years, with CAH; 62% of the patients had salt wasting (26), 33 % simple virilizing (14) and 5 % nonclassical form (2). The median age was 9 years [7-12]. The study included a clinical examination, hormonal profile and scrotal grayscale and color Doppler ultrasonography. Bone age was defined using Greulich-Pyle method.
Results: All patients were divided into 2 subgroups: patients in the first group were treated irregularly (absence of therapy more than 6 months), patients in group 2 had good compliance and regular treatment.

	Patients	CAH form (SW/SV/NC)	median of age, years	Length of time without treatment	Median of growth SDS	Median of bone age / age ratio	Number patients with TART
Group 1	21	5/14/2	9 [7;9]		+2.2 [0.7;3.3]	1.5 [1.3;1.8]	19% (4/ 21)
		5 - SW		1.5 [1.0;2.4]		1.9	4
		14- SV		4.6 [4.0;6.7]		1.5	
		2 - NC		7.0[5.5;8.5]		1,3	
Group 2	21	21 - SW	9 [7;14]		-0.1 [-0.9; 1.1]	1 [1;1.17]	5% (1/ 21)

[Table 1]

In the whole group TARTs were found in 12% of cases (5/42). All patients with TARTs had SW form, regardless of the fact of patients with SV and NC form had longer period of decompensation. 4 patients with TARTs had late diagnosis and irregular treatment, but one had good compliance and regular treatment. TARTs were not palpable, all of them were detected by ultrasound. All TARTs were bilateral, located closer to the mediastinum testis, hypoechoic and had indistinct boundaries.
Conclusions: According to our data TARTs were found only in patients with SW CAH who had irregular treatment excepting for 1 patient. This may be explained by important role of Angiotensin 2 in decompensated SW CAH patients, though should be other factors that demand farther investigation.

P2-d1-659 Adrenals and HPA Axis 7

Neonatal massive bilateral adrenal **haemorrhage associated with subclinical hypoadrenalism spontaneously recovering**

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Background: Neonatal adrenal hemorrhage (NAH) is an unusual condition affecting 0.2% of newborn. Adrenal hemorrhage etiology has been associated with traumatic delivery, hypoxia, shock, septicemia, and bleeding diathesis.
Objective: We report a case of a baby girl with atypical presentation at diagnosis of NAH.
Method: At birth she was born by vaginal delivery with vacuum extraction at 41st week, her weight was 3730g. At 8th day of life an ultrasound of the abdomen was performed for a suspected urinary tract infection with high PCR values that revealed a bilateral large adrenal hemorrhage. The infant never exhibited clinical signs of adrenal insufficiency. An ACTH provocative test (0.25 mg iv) on 25th day of life revealed a baseline cortisol serum level of 2.5 mcg/dl, which increased to 9.7 mcg/dl within 30 min after the test (nv >18.1), baseline ACTH was 119 pg/ml (nv < 46 pg/ml). Hydrocortison replacement therapy was then suggested and never started for the parents' decision; later on the patient came to our centre. Blood sample performed at our centre, at 40 days of life, showed cortisol 13.3 mcg/dl; ACTH 132 pg/ml; K 5.9 mEq/l and altered ACTH provocative (cortisol peak 10.2 mcg/ml) suggesting subclinical hypoadrenalism with no clinical features. So it has been decided to do not start hydrocortison therapy.
Results: Serial ACTH provocative tests showed a progressive improvement of cortisol levels and adrenal imaging with normalization at 10th month of life. Last ACTH provocative test at age of 20 months revealed that the adrenals function was normal, basal cortisol level was 11.4 mcg/dl, and after ACTH stimulation it run up to 30.3 mcg/dl (basal ACTH was 12 pg/ml).
Conclusions: Our case showed the spontaneous total recovery of hypoadrenalism after adrenal hemorrhage at birth in a baby girl without any treatment in the first year of life.

P2-d1-660 Adrenals and HPA Axis 7

Clinical and biochemical characteristics of classic 21-hydroxylase deficiency patients with central precocious puberty

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Background: Central precocious puberty (CPP) is a common problem in classic 21-hydroxylase deficiency (21-OHD), but its characteristics and gonadotropin response to GnRHa in these patients are not well described.
Objectives:
(1) To study the clinical and hormonal characteristics of classic 21-OHD patients with CPP,
(2) to compare gonadotropin response after GnRHa test in these patients with pubertal-matched controls and
(3) to study the height outcome after GnRHa treatment.
Methods and results: Sixteen classic 21-OHD patients with CPP were retrospectively assessed. Mean ages at pubertal onset were 6.45±1.24 yr. Advanced bone age (BA) and poor predicted adult height (PAH) were observed before GnRHa treatment (mean BA 11.48±1.69 yrs, and mean PAH-SDS -2.94±1.78). After GnRHa stimulation, most cases showed pubertal response (peak LH > 6 IU/L) but there were 3 patients who had prepubertal response but eventually had pubertal progression after 6 mo follow-up. Baseline 17-hydroxyprogesterone (17-OHP) levels were significantly different between groups [median 17-OHP were 13,895.4 (6,641-18,480) in prepubertal response group *vs.* 3,700 (82-9,580) ng/dL in pubertal response group; $P< 0.05$]. Gonadotropin response to GnRHa stimulation in 21-OHD patients was compared with controls. Baseline LH, peak LH and LH:FSH ratio were not different between groups. 14 cases were treated with monthly GnRHa. Mean PAH-SDS was significantly improved (mean PAH-SDS at baseline were -3.08±1.08 *vs.* at stopped treatment -1.53±1.82; $P< 0.05$). Only 4 cases reached final height (FH), mean FH was higher than PAH at pubertal onset but did not reach statistical significance (PAH-SDS -2.92±0.75 *vs.* FH-SDS -1.40±1.01).
Conclusion: CPP commonly occurs after treatment in classic 21-OHD. GnRHa test in these patients should be interpreted cautiously as gonadotropin response could be subnormal in poorly hormonal-controlled patients. GnRHa therapy appears to improve height outcome in 21-OHP patients with CPP.

P2-d1-661 Adrenals and HPA Axis 7

Variable manifestation of **pseudohypoaldosteronism type 1b in consanguineous brothers**

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Introduction: Pseudohypoaldosteronism type1b(PHA1b) is a rare multisystem disorder characterised by hyperkalaemia, hyponatraemia and metabolic acidosis. Aggressive salt replacement and control of hyperkalemia results in survival. PHA1b results from a loss-of-function mutation in the epithelial sodium channel(ENaC).
Case study: We report a variable presentation of PHA1b of brothers from a consanguineous Pakistani family. The index case(23months old) presented at 2weeks with vomiting and lethargy secondary to Klebsiella urinary tract infection. His sodium and potassium were 129mmol/L and 7.6mmol/L respectively suggesting secondary PHA precipitated by the UTI. However, the electrolyte disturbance persisted after 7days of antibiotic therapy. 17-hydroxyprogesterone and cortisol were normal but aldosterone(40,800pmol/L) and renin(194nmol/L/hr) were significantly elevated. His sweat test showed increased sweat Sodium(177mmol/L) and Chloride(149mmol/L) consistent with PHA1b. He required up to 50mmol/kg/day of sodium supplements,calcium resonium and potassium free diet to maintain electrolyte homeostasis. At 2 months he presented with sodium of 119mmol/L and potassium of 10.1mmol/L precipitated by vomiting leading to ventricular fibrillation requiring intensive care.He remains on 30 mmol/kg/day of sodium supplementation and is developing well. His 4 month old brother presented at 5 days of age with profoundly resistant hyperkalemia and arrhythmia. His

potassium was >10mmol/l requiring 70 mmol/kg of intravenous sodium chloride with insulin/glucose and bicarbonate infusion to achieve stability. Serum potassium reduced to normal after 24 hours of intensive therapy. He remains well controlled on sodium supplements and a low potassium feed.Genetic analysis confirmed SCNN1A mutation resulting in a loss of function mutation of ENaC.
Conclusion: Pseudohypoaldosterinosm can be life threatening with rapid deterioration requiring close monitoring and early intervention during illness.

P2-d1-662 Adrenals and HPA Axis 7

Genotype-phenotype correlations in Turkish children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Background: Congenital adrenal hyperplasia (CAH) resulting from mutations in the 21-hydroxylase gene (CYP21A2) accounts for 90-95% of all cases. There is a strong relationship between genotype and disease severity.
Objective and hypotheses: The aim of the study was to investigate the most frequent, well-known mutations in CYP21A2 and to describe the genotype-phenotype correlation in Turkish children with CAH due to 21-hydroxylase deficiency.
Methods: The phenotypic classification of CAH was based on clinical and hormonal criteria. Genetic analyses performed using a reverse-hybridisation test strip-based assay covered the 11 most prevalent CYP21A2 mutations in European populations: P30L, IVS2 splice (IVS2 G), Del 8 bp E3 (G110del8nt), I172N, Cluster E6 (I236N, V237E, M239K), V281L, L307 frameshift (F306+T), Q318X, R356W, P453S, and R483P.
Results: Mutational analyses were performed in 38 patients and 10 family members. Fifteen patients suffered from the salt wasting (SW) form, 10 from the simple virilising (SV) form, and 13 from the nonclassical (NC) form. Mutations were detected in 31 of the 38 patients (81 %) and 9 of the 10 family members (90 %). The most frequent mutations were point mutations (93 %), followed by splice site mutations (51 %) and deletions (25 %). IVS2, IVS2+P30L+del 8 bp, IVS2+P30L+del 8bp+V281L, R356W, E1-E6 del, IVS2+Q318X and Q318X mutations were found in SW form. IVS2, IVS2+V281L, IVS2+P30L, IVS2+del 8bp and Q318X mutations were found in SV form. IVS2+P30L+del 8bp, IVS2+P30L+del 8bp+V281L, P453S, V281L, P30L, Q318X mutations were found in NC form.
Conclusions: This study showed a correlation between genotype and phenotype in patients with 21-hydroxylase deficiency. The results suggest that well-known mutations can predict disease severity. Genetic analyses are an important confirmatory tool for early and reliable diagnosis of CAH.

P2-d1-663 Adrenals and HPA Axis 7

Successful treatment of childhood recurrent Cushing disease after trans-sphenoidal surgery with different treatment modalities: long-term follow-up

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Background: Although primary treatment of Cushing's Disease (CD) is transsphenoidal surgery (TSS), other therapy modalities such as gamma knife radiosurgery (GKRS) and medical treatment should be considered in recurrent CD. We present successful treatment of two patients with recurrent CD with GKRS and cabergoline.
Case 1: 8 $^{3/12}$ years-old girl admitted with rapid weight gain and hypertension. Clinical features and hormonal workup revealed ACTH-dependent CD. Pituitary MRI revealed suprasellar 15x9x10 mm adenoma, and TSS was performed. 15 months after TSS, CD recurred as shown by overnight-dexamethasone-suppression-test (ODST) and urinary free cortisol (UFC) levels. Since there was no residue tumor in MRI, inferior petrosal sinus sampling (IPSS) was performed and ACTH gradient was found in left side. GKRS was applied to the left side of sella turcica and cavernous sinus. 20 months after GKRS, UFC and ODST showed recurrence of disease. Second IPSS showed ACTH gradient was insisting in left side and GKRS was applied to all intrasellar area. Subsequently hypothyroidism and growth hormone deficiency was developed and treated. At the age of 14 $^{4/12}$ years she had recurrence again. Cabergoline was started 1mg/weekly and she was cured as shown by ODST.
Case 2: Female patient diagnosed as metabolic syndrome at the age of 14 $^{9/12}$ years, was investigated regarding headache and blurred vision of the left eye at the age of 15 $^{2/12}$ years. Hormonal workup revealed CD and MRI showed an adenoma in the left side of pituitary gland (7x4 mm). TSS was applied and 16-months after the surgery UFC level increased. Since there was no apparent tumor in MRI, IPSS was performed with 7 fold increase in ACTH in both sides of the pituitary gland. GKRS was applied at 17 years of age. 12-months after GKRS, ODST and UFC levels were still normal.
Conclusion: In patients with recurrent CD after TSS, treatment with GKRS and cabergoline is successful in long term.

P2-d1-664 Adrenals and HPA Axis 7

Atypical clinical presentation of ACTH dependent Cushing syndrome in a patient treated with retinoic acid

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Introduction: Cushing's syndrome (CS) is one of the rarest endocrinopathies occurring in adolescents. It is most often caused by an ACTH-secreting pituitary adenoma. Its symptoms depend on the duration and severity of cortisol and androgen excess.
Case study: 17.5 year old boy treated for 12 months with retinoic acid (40 mg daily) because of severe acne was admitted due to: short stature (-3.0 SD), muscle weakness and impaired concentration. There was no obesity (BMI 22 kg/m2), hypertension (BP 120/70 mmHg) nor disorders of puberty. Blood glucose and lipids levels were normal. Bone mineral density was decreased (Z-score - 3.5 SD). Morning serum cortisol level was normal (171.9 ng /ml), with no decrease in the evening (178.9 ng / ml) nor after 1 mg of dexamethasone (100.4 ng /ml). Urinary free cortisol was incresed (274.5, 217.3, 253.7 ug / day). The concentration of plasma ACTH was increased (morning 97.5 - 141.1 pg / ml) and after stimulation with CRH (577.6 pg /ml). MR imaging revealed pituitary microadenoma (2.5 x 2 mm). The atypical clinical picture of ACTH dependent CS may correspond to the retinoic acid, which may be a limiting factor inhibiting the secretion of ACTH and adrenal steroidogenesis. It could partially abolish results of cortisol and androgen excess and prevent the development of more severe the symptoms (obesity, hypertension), but not the symptoms depending on the lower concentrations of cortisol (reduced growth velocity, decreased muscle strength and bone mineral density, symptoms of central nervous system dysfunction) and androgen-dependent (bone age advance, acne, androgenic hair).
Conclusion: Before introduction of treatment with retinoic acid in patients with severe acne ACTH-dependent CS should be ruled out as a cause of hyperandrogenism. Retinoic acid can alter the clinical presentation and delay the proper diagnosis and treatment.

P2-d1-665 Adrenals and HPA Axis 7

A challenging early diagnosis in a case of prepubertal Cushing disease

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Background: Cushing's disease is very rare in children. The highest incidence is at 14.1 years. From the first symptoms to diagnosis it takes on average 2.5 years.
Objective: To report a case of prepubertal Cushing's disease that highlights the diagnostic difficulties in children's Cushing's disease at an early stage.
Case presentation: In an 8-year old prepubertal boy a rapid weight gain of app.10 kg within the last 9 months accompanied by a decreasing growth velocity and hirsutism but without any other signs or symptoms was observed. Height SDS was -0.14 and BMI-SDS was +1.28. To confirm Cushing's syndrome, we performed the following investigations: 24-hour urinary free cortisol levels were consistently elevated in three independent measurements. The assessment of diurnal plasma cortisol levels revealed an increase of cortisol levels, however, a circadian rhythm was still preserved. Low-dose dexamethasone suppression test showed a lack of suppressibility of cortisol. The excretion rate of glucocorticoids in the urine steroid analysis was only 2.5-fold increased with urine free cortisol being 10-fold above the reference range suggesting the beginning of an increased endogenous cortisol production. Further tests to confirm the suspected diagnosis Cushing's disease showed the following results: Basal morning ACTH was in the normal range. High dose dexamethasone suppression test led to a decrease of morning cortisol by only 51%. In the CRH test, serum ACTH and cortisol increased only by 28%. Repeated magnetic resonance imaging finally revealed a 3 mm microadenoma in the anterior pituitary. The patient underwent transsphenoidal surgery. Histopathological analysis confirmed an ACTH-secreting pituitary adenoma.
Conclusion: This case illustrates the difficulties associated with the biochemical and radiological diagnosis of Cushing's disease in children. Diagnosis at an early stage of disease remains challenging as test results do not match standard diagnostic criteria.

P2-d1-666 Adrenals and HPA Axis 7

Tall stature in two sisters with a homozygous mutation in the CYP17A1 gene

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Background: Steroid 17 α hydroxylase / 17,20 lyase deficiency (17 OHD) is due to mutation in the CYP17A1 gene. The characteristics of 17 OHD include hypertension, hypokaliemia, delayed puberty due to deficient sex hormone synthesis, and in XY individuals, disorder of sexual differentiation with a female phenotype.
Objective and hypotheses: To present two sisters with 17 OHD, delayed puberty and tall stature. We hypothesised that deficient skeletal maturation and continuous growth were due to estrogene deficiency.
Patients and methods: Two sisters were admitted at the age of 13.8 and 16.7 years due to delayed puberty. Both had hypertension and hypoka-laemia and female karyotype, 46,XX. The CYP17A1 gene (exon 1-8) was DNA sequenced.
Results: At admission heights were 175 cm and 178 cm (the older sister). Parents were healthy, Caucasian and non-consanguineous. Parents height were 195 cm and 169 cm, with target height 175.5 cm. A healthy sister was 179 cm 21 years old. Both girls were prepubertal, Tanner stage B1 and P1, and bone age was 7.1 and 9.5 years, respectively. Internal genitalia were prepubertal on magnetic resonance imaging. Adrenocorticotropic-hormone, progesterone, corticosterone, luteinizing-hormone and follicle-stimulating-hormone were elevated. Dehydroepiandrosteronsulfat, androstendione, testosterone and estradiol were undetectable. A known homozygous mutation in the CYP17A1 (c.287G>A)(p.Arg96Gln) was detected. Treatments were hydrocotisone, transdermal estradiol, spironolactone and dihydroepiandrosteron. After two years of treatment the height of the younger sister was 184 cm, bone age was 12.4 years and estimated final height was 191.8 cm. Height of the older sister was 183 cm, bone age was 14 years and estimated final height was 186.2 cm.
Conclusion: Girls with 17OHP and total estradiol deficiency do not spontaneously enter puberty. Bone age may be severely retarded. If not timely treated with estradiol these patients may end up with tall stature.

P2-d1-667 Autoimmune Endocrine Diseases 2

Total body bone mineral density, total body bone mineral content and body composition in children with type 1 diabetes

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Background: There is still small clinical information's about body composition and skeleton status in children with IDDM and factors influenced on.
Objective and hypotheses: To asses body composition, skeleton staus in IDDM children and factors influenced on.
Methods: BMD, BMC (TBBMD, TBBMC, L24BMD, L24BMC) and body composition (LBM, FM) were measured by DXA in 60 children (33 girls and 25 boys) with IDDM since 5,09 years± 3,95t (min.1,0, max. 11,8), aged 15,03±1,95t (11,4-17,8), age of beginning IDDM 9,98±3,90 (2,5-17,0) and mean metabolic control in last year -HbA1c-7,8 ±1,7 (5,1-13,6). Results were compared to own laboratory norm for age and sex. TBBMC/LBM, L24BMC/LBM, FM/LBM ratios were also calculated and correlations between this factors and age, age of beginning IDDM and duration of illness.
Results: IDDM patients have significant lower BMD and BMC for total skeleton, L24 lumbar spine, worse TBBMC/LBM and L24BMC/LBM ratios, more fat tissue and more fat tissue percentage participation in body composition. FM and LBM correlated with TBBMD, TBBMC, L24BMD, L24BMC, FM/LBM TBBMC/LBM, and L24BMC/LBM ratios. TBBMD and TBBMC correlated each other and with LBM, FM, L24BMD, L24BMC, TBBMC/LBM and L24TTBMC/LBM ratios. Only LBM correlated with HbA1c. There were no correlations with duration of IDDM and age of beginning of illness.
Conclusions: LBM is the crucial factor in metabolic control and skeleton status in children with IDDM.

P2-d1-668 Autoimmune Endocrine Diseases 2

Cardiovascular risk evaluation in a type 1 diabetes paediatric population and comparison with a control cohort

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Background: The aim of this study was evaluation of cardiovascular risk (CVR) associated with Type 1 Diabetes (T1DM) in children.
Methods: We studied 188 T1DM children (88 females), and 1317 healthy children (631 females), aged 5-15 years.
Familiar, medical and clinical data were collected by standardized methods and CVR were analysed according to European Society of Hypertension (2009).
Results: T1DM children showed a lower rate of overweight/obesity, low birth weight and central adiposity than healthy controls. Frequency of hypertension was similar in the two groups. Mean systolic (SBP) and diastolic (DBP) blood pressure percentile of T1DM group was significantly higher. There was no

gender difference in overweight / obesity, hypertension and central adiposity. There was a lower frequency of first-degree family history of cardiovascular disease (2.1 vs. 6.1%, p 0.02) and dyslipidemia (12.8 vs. 22.6%, p 0.002) but not of hypertension (16.0 vs. 19.2%, p 0.29). BMI showed a positive correlation with SBP (r 0.23, p 0.0014) and HDL values (r-0.16, p 0.037).
Conclusions: Our findings show a lower prevalence of CVR factors in T1DM children but a similar prevalence of hypertension and significantly higher SBP and DBP. This suggests a possible condition of iatrogenic hyperinsulinism which may increase blood pressure.

P2-d1-669 Autoimmune Endocrine Diseases 2

Polyglandular autoimmune syndromes type III in children with type 1 diabetes mellitus

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Background: Type III PAS is composed of autoimmune thyroid diseases associated with endocrinopathy other than adrenal insufficiency. This syndrome is associated with organ-specific and organ-nonspecific or systemic autoimmune diseases. The frequency of PAS syndromes in diabetic children is unknown.
Objective and hypotheses: The aim of the study was to evaluate the incidence of PAS III in children with diabetes mellitus type 1.
Methods: The study included 461 patients with diabetes mellitus type 1(T1DM), who were 1-19 years of age. TSH, free thyroxin, TPO autoantibodies, and thyroglobulin autoantibodies were determined annually. Autoimmune Hashimoto's thyroiditis was diagnosed in children with positive tests for TPO Ab and Tg Ab and thyroid parenchymal hypogenicity in the ultrasound investigation. Elevated TSI antibodies were used to diagnose Graves' disease. Additionally, Anti-Endomysial Antibodies IgA class were determined every year as screening for celiac disease. During clinical control other autoimmune diseases were diagnosed. The adrenal function was examined by the diurnal rhythm of cortisol.
Results: PAS III was diagnosed in 14,5% children: PAS IIIA (T1DM and autoimmune thyroiditis) was recognized in 11,1 % and PAS III C (T1DM and other autoimmune disorders: celiac disease, and JIA, psoriasis and vitiligo) in 3,5% children. PAS IIIA was more prevalent in girls than in boys - 78,4% versus 21,6% (p< 0,05). PAS III was observed between 1-5 years of life in 66,6% children; the frequency decreased in consecutive years and successively increased in the adolescence period to 22,7%.
Conclusions: PAS III occurs in 14,5% of children with DM type1 and incidence is positively correlated with patients' age and with the female gender. The children with PAS III should be carefully monitored as the risk group of other autoimmune disease development.

P2-d1-670 Autoimmune Endocrine Diseases 2

The incentive trial: do financial rewards improve glycaemic control in teenagers with poorly controlled type 1 diabetes?

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Background: Adolescence is recognised as a period where compliance to diabetes treatment is challenging. During this period young people assume increasing responsibility for their diabetes self-management.
Objectives and hypothesis: Giving modest financial rewards will motivate teenagers with Type 1 diabetes to improve their glycaemic control.
Population and methods: Population; young people with Type 1 diabetes, age 13 to ≤ 15 years at entry, duration of diabetes of >2 years and sustained HbA1c level of > 9% for >6 months.
Young people were identified from clinic lists and recruited to the study.
Retinal screening and an educational refresher on hypoglycaemia was provided.
All patients received routine care and monitoring.
Patients received a £10 gift voucher for every 0.5% drop in HbA1c. This reward was summative until an HbA1c of 7.5% was achieved. A maintenance voucher of £10 was given if HbA1c continued to be < 8.0%. If the HbA1c increased participants were only eligible for further financial rewards after they returned to their previous best HbA1c level.
The vouchers were given to the young person at each clinic visit if they fulfilled the criteria.
Results: The study included 17 participants (10 male, 7 female) with an age range of 13 to 15 years (median 14 years).

Time (Months)	HbA1c (%)(Range)	p value
0	10.4 (9-12.1)	
3	9.9 (7.8-12.6)	0.18
6	9.9 (7.2-14)	0.38
9	9.6 (8.8-11.9)	0.03
12 (End)	9.9 (8.3-12.9)	0.21
3 (post study)	10.4 (8.7-12.2)	0.92
6 (post study)	10.2 (8.3-14.1)	0.73
12 (post study)	10.4 (7.7-14.9)	0.94

[Table 1: The group mean HbA1c]

Receivers of vouchers (n=11) showed an overall fall in HbA1c (10.8 to 9.8) and for non-receivers (n=6) the HbA1c increased (9.6 to 11.6).
Conclusions: In this cohort financial incentive did not lead to improvement in HbA1c.

P2-d1-671 Autoimmune Endocrine Diseases 2

High prevalence of negative islet autoantibody status in children with type 1 diabetes in a region of inner city London

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Background: It is important to clearly define diabetes sub-type in a child presenting with diabetes as prognosis, care processes and treatments vary accordingly. Islet autoantibody levels aids the diagnosis of diabetes sub-type, and knowledge of the limitations of the assays routinely used in clinical practice to measure these autoantibodies is important.
Objective and hypotheses: To prospectively determine the islet autoantibody status in children presenting with diabetes in relation to clinical features and changes in the assay used.
Methods: Data were prospectively collected on 240 children diagnosed with diabetes between 2006 and 2011 in two neighbouring centres in inner-city London, all of whom were initially tested for islet cell antibody (ICA) and Glutamic Acid Decarboxylase 65-kDa (GAD65), and if negative for both, tested for IAA autoantibodies. For GAD65 autoantibody testing, two different methods were used in our laboratory for the duration of our study.
Results: 94 (39.2%) children tested negative for the three autoantibodies. Of these, children assigned a diagnosis of T1D (n=83, 88.8%) compared to T2D (n=11, 11.2%) were more likely to be younger, female, white and thinner at presentation and remained thinner and had greater reduction in HbA1c levels during follow-up (-0.7% [95% confidence interval -0.9 to -0.4] versus (-0.2% [-2.0 to 1.6], P< 0.001). No ethnic differences were observed. Only 15.7% of the whole cohort were GAD65 positive. No significant difference existed in the rate of GAD65 positivity using radioimmunoassay compared with indirect immunofluorescence.
Conclusions: Our results suggest that a more sensitive method than either radioimmunoassay or indirect immunofluorescence is required to measure GAD65 and consideration should be given to measuring alternative islet autoantibodies.

P2-d1-672 Autoimmune Endocrine Diseases 2

Proinflamatory cytokines (IL-1β and TNF-α) in childhood autoimmune thyroid diseases

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Introduction: Chronic autoimmune thyroiditis (cAIT) and Graves' disease (GD) are the most common autoimmune disorders in children. cAIT, due to T cell-mediated cytotoxicity leads to hypothyroidism in most cases. In contrast, GD and its thyrotropin receptor stimulatory autoantibodies generates hyperthyroidism. Cytokines play a crucial role in modulating immune responses in both these disorders.
Materials and methods: We studied serum IL-1β and TNF-α (ELISA) in 22 newly diagnosed children with cAIT(mean:TSH 46,7μIU/mL↑, fT4 0,54 ng/dL↓, fT3 2,10 pg/mL;ATPO 2597 IU/mL↑, ATG 533 IU/ml↑),22 newly diagnosed GD(mean:TSH 0,01 μIU/mL↓, fT4 4,24 ng/dL↑, fT3 19,01 pg/mL↑; TRAb 24 U/L↑ ATPO 2280 IU/ml↑, ATG 426 IU/ml↑) and 20 healthy subjects with normal fT4, fT3, TSH and negative antithyroid Abs.
Results: TNF-α levels did not differ significantly between all groups {cAIT(median; IQR)15,08 pg/ml;21,94), GD(13,63 pg/ml;15,28) vs control(0,96 pg/ml;12,81)(p=0,067)}. IL-1β concentration was significantly higher in cAIT(2,16 pg/ml;0,87) vs control(1,88 pg/ml;1,04)(p< 0,05) and cAIT vs GD(1,39 pg/ml;1,27)(p< 0,01).
Significant positive correlations between cytokines were identified in cAIT: IL-1β and TNF-α(r = 0.45,p< 0.05). TNF-α positively correlated with ATPO in cAIT(r=0,54;p< 0,01), as well as IL-1β and ATPO in GD(r =0,47;p< 0,05). ROC curve indicates that both, IL-1β and TNF-a, exhibit a good discriminatory efficacy between healthy and cAIT children (IL-1β: AUC=0,77; p=0,003; TNF-α: AUC=0,691; p=0,034) with low sensitivity (IL-1β. 59,1%;TNF-a 54,5%) but high specificity(IL-1β 95%;TNF-a 85%).
Moreover, the ROC curve for IL-1 β showed good sensitivity and specificity to discriminate between group of cAIT and GD (IL-1β: AUC=0,773;p=0,002) (sensitivity:72,7%;specificity:86,4%).
Conclusions: Both, IL-1β and TNF-α, could efficiently discriminate healthy and autoimmune-hypothyroid children. Serum IL-1β levels were significantly higher in cAIT and may be used for differentiating cAIT from GD.

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Autoimmune hypoparathyroidism as the only clinical manifestation of autoimmune polyglandular syndrome type 1 (APS-1): a case report

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Introduction: Common features of APS-1 include candidiasis, hypoparathyroidism and hypoadrenalism. The initial manifestation may be candidiasis, hypoparathyroidism and later autoimmune adrenal insufficiency. Children and adolescents from Iranian Jewish, Sardinian, and Finnish populations have been associated with APS-1 more often.
Case study: We discuss an 11-year-old girl of Ashkenazi Jewish descent who presented at 3.5 yrs of age with seizures and prolonged QTc secondary to severe hypocalcemia 5.9 mg/dl, elevated Ph at 9.5 mg/dl, low PTH < 3 pg/ml 9 (10-65pg/ml), and low 25OH-vitamin D at 19 ng/ml. Antibodies (AB) against calcium-sensing receptor (CaSR) were negative, only AB against interferon omega were positive. There was no evidence of alopecia, vitiligo or candidiasis. She had dental caries without enamel hypoplasia.
She was followed in our clinic the last 9 yrs with yearly screening for 21-OH AB, adrenal AB, Islet cell AB, GAD AB, celiac screen, TPO and TG AB, CBC, LFTs, growth rate evaluation; all data were normal.. Family history was not contributory. The patient was found to be positive for a de novo mutation of exon 8 of AIRE gene, and subsequent search for the mutation in her parents and 3 siblings was negative.
She was treated with calcium supplement and calcitriol. In the first 3 yrs after diagnosis levels of calcium was fluctuating, but the last 5 yrs they had been stable.
Conclusion: This case is unusual that in a big family this is *de novo* mutation, presented with only isolated autoimmune hypoparathyroidism, without AB, except AB against interferon omega. APS I, usually occurs in children aged 3-5 years or in early adolescence, sometimes decades may pass before the appearance of new symptoms. We consider that lifelong follow-up is necessary, because unrecognized adrenal insufficiency can be life-threatening. AIRE gene evaluation in cases of isolated hypoparathyroidism is important because it can impact on follow up routines.

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Fulminant type 1 diabetes mellitus and chronic mucocutaneous candidiasis with *STAT1*-mutation: a case report

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Background: Fulminant type 1 diabetes mellitus (FT1DM) is a unique subtype of type 1 diabetes, characterized by abrupt onset of diabetic ketoacidosis (DKA), almost entire destruction of pancreatic beta cells and absence of islet-related autoantibodies. FT1DM accounts for approximately 20% of acute onset type 1 diabetes in Japan, but is reported to be rare among children. On the other hand, chronic mucocutaneous candidiasis (CMC) is characterized by candidiasis of the nails, oral or genital mucosa, caused by inborn errors of IL-17 immunity. In 2011, the gain-of-function mutation of *STAT1* gene was reported to cause CMC. We here report a girl who presented FT1DM and CMC from her early infancy, proved to be with *STAT1* mutation.
Case study: The patient was first referred to our hospital at the age of 4 years for the purpose of controlling type 1 diabetes. She was born full-term and neonatal course was uneventful except for mild umbilical infection. Oral candidiasis was sometimes found, which was treated successfully with topic anti-fungal ointment. When 3-month old, she presented sudden onset of DKA with HbA1c (NGSP) 6.7% and negative anti-glutamic acid decarboxylase antibody. From the onset, she was treated with insulin infusion, and later was switched to insulin pump therapy. C-peptides were undetectable in her early phase of diabetes. Because she repeated various bacterial infections and candidiasis, we conducted genetic analysis and found heterozygous mutation in *STAT1* (M202T), not in her parents and sister.
Conclusion: This is the first report of the case with FT1DM and CMC. Of interest, she developed FT1DM-like symptom from early infancy, which is extremely rare even among Japanese, and might be related to an innate disorder of autoimmunity, CMC. We will evaluate the long-term outcome, including other autoimmune disease reported to be concurrent with CMC. Further studies are needed to elucidate cytokine networks which are related to pancreatic beta-cell apoptosis.

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Role of C-peptide in the pathogenesis of microvascular complications of type 1 diabetes with paediatric age onset

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Background: Patients with type 1 diabetes mellitus tend to develop vascular complications as a consequence of scarce glycometabolic control and genetic predisposition; other factors may however concur.
Objective: We analyzed the potential protective effect of C-peptide (produced by βcells in equal molarity to insulin) against the development of diabetic nephropathy and retinopathy. Former studies showed that in some patients with over 20 years of diabetes it is possible to detect a residual C-peptide

secretion; C-peptide was shown to be an independent hormone with an active biological role.
Methods: We followed a cohort of type 1 diabetic patients with onset at pediatric age, a 6 years minimum of disease duration and C-peptide measured one year after onset. We monitored renal function and eye fundus in two occasions (disease duration of 11,4 (±4,5 SD) and 18 (±8,5 SD) years).
Results: First evaluation point: low C-peptide precedes the development of microalbuminuria (p=0.03) and retinal microaneurisms (p=0.02). Retinopathy also appears to be influenced by glycometabolic control (p=0.03), blood pressure (p=0.04 for SBP; p=0.02 for DBP) and blood lipids (p=0.001). There was no correlation between C-peptide secretion and HbA1c values, suggesting the protective effect of C-peptide not being consequence of residual insulin secretion.Second evaluation point: the C-peptide protective effect was no more significant. Similarly, the protective effect of glycometabolic control on the development of retinopathy was lost (probably because of the progressive disappearance of the metabolic memory).
Conclusions: These observations suggest a possible protective effect of C-peptide on the development of nephropathy and retinopathy in the early stages of diabetes. Along with glycemic, blood pressure and blood lipid control, a residual C-peptide secretion could have a role in delaying the onset of microvascular complications in type 1 diabetes.

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Incidence and trends of childhood (age 0-14 years) type 1 diabetes in Lombardy from 2002 to 2007

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Objective: To examine the incidence and trends of Type 1 diabetes mellitus (T1D) in Lombardy from 2002 to 2007 in children (ages 0-14 years).
Methods: The incidence of T1D (per 100.000/year) was evaluated in children in Lombardy from 2002 to 2007. Two independent sources were used. The primary source consisted of prescription data collected from Regional Institutions. The secondary source consisted of new cases of T1D diagnosis according to ADA criteria from three Lombard hospitals (San Raffaele of Milano, AO Spedali Riuniti of Brescia, Ospedale del Ponte of Varese). Hospital registries were prospective and/or retrospective. The data sources contained information on sex, address, age at diagnosis and date of birth. The two dataset were compared and found almost identical (case ascertainment >95%). Incidence rates and 95% CI were calculated assuming the Poisson distribution. Trend of type 1 diabetes incidence was analyzed using the Poisson regression model.
Results: A total of 1136 new cases of T1D were diagnosed in a children population (mean population 0-14 years in the study period: 1.251.000). Incidence rate was 14,48/100.000 in 2002, 16,70/100.000 in 2003, 14,62/100.000 in 2004, 15,40/100.000 in 2005, 12,99/100.000 in 2006, 16,55/100.000 in 2007. Age- and sex- adjusted incidence did not changed significantly during the observed years, although the 0-4 class showed a significant decrease relative to 10-14 class (OR=0.91 95% CI= 0.83-0.99).
Conclusion: T1D mean incidence rate in Lombardy (2002-2007) has increased by approximately two-fold compared to EURODIAB study (1989-1994, mean incidence 7.0/100 000). However, there was no significant increase from year 2002 to 2007. Furthermore, a significant decrease in incidence rate was found in the 0-4 range. Further studies are needed to clarify the actors contributing to region-specific trends in T1DM incidence.

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Peer review: a tool to improve paediatric diabetes services

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Background: Peer Review programmes (PRP) help organisations to improve the quality of clinical services in a supportive way. The West Midlands Paediatric diabetes network consists of 15 hospital Trusts looking after 2,800 children (aged 0-18 years). 2010/2011 National Paediatric diabetes audit (NPDA) showed that the median HBA1c achieved in the region was 73mmol/mol. Only 5% of children nationally had all care processes documented. In order to improve the metabolic control and quality of care, the network embarked on a PRP.
Objective and hypotheses: To provide benchmark data which will act as a catalyst for service improvement.
Methods: Following development of network quality standards and formal training of the diabetes team, parents and commissioners as reviewers, all the Trusts completed a self assessment. This was followed by review visits (Sept. 2012-march 2013) assessing all aspects of the patient journey. During the visit of facilities; patients, parents, doctors, nurses,dieticians and managers are interviewed. Results of visits are sent to Trust chief executives and will be made public.
Results: 12/15 Trusts have had visits. The median level of compliance following visits was lower than self assessment of compliance (62% versus 84%). 75% did not have adequate specialist nursing /dietetic staff for the number of children in their caseload. 66% did not offer regular structured group patient education on an ongoing basis.58% did not have robust arrangements for ensuring all children received all care processes as defined by NPDA. Transition arrangements were judged inadequate in 50%. Examples of good practice noted during the visits (which will be shared at a network event) include examples of excellent patient information, provision of 24 hour helpline, examples of structured approach to care planning.
Conclusions: The PRP has enabled the network and Trusts to identify areas of service that need improvement. The PRP is now being rolled out nationally.

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22q11.2 microdeletion syndrome: analysis of 7 children diagnosed in a tertiary hospital

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Background: The 22q11.2 deletion syndrome is a contiguous gene deletion syndrome with an incidence rate of 1/4,000-6,000 live births. The clinical features are: congenital conotruncal heart diseases, palate anomalies, endocrine abnormalities (hypocalcaemia due to primary hypoparathyroidism, short stature and thyroid dysfunction), immunity problems, learning difficulties, mental retardation and a facial dysmorphisms (long narrow face, upslanting palpebral fissures, hypertelorism, tubular nose with bulbous nasal tip and small mouth and ears).
Objective and hypotheses: To review the clinical features of children with 22q11.2 deletion syndrome diagnosed at our hospital between 2004 and 2012.
Methods: Retrospective study of 7 patients with 22q11.2 deletion syndrome diagnosed at our hospital in the time period 2004-2012. Variables analyzed: age and sex at diagnosis, presenting phenotype, clinical features and positive family history.
Results: Age at diagnosis ranged from new born to 12 years, with a predominance of the male over the female proportion of 3'5:1; three of the seven patients were diagnosed in the first month of life.Clinical features: all patients had characteristic facial features; congenital heart disease (71.4 %), velopharyngeal incompetence (57.1 %), developmental delay and learning difficul-

ties (85.7%), hypoparathyroidism (42.8%), renal and urogenital anomalies (28.5%), short stature (28.5%) hearing deficits and hypothyroidism (14.2%); any patient presents immune alterations.
All of the deletions were de novo, except in one case where was desconocian the biological parents.
Conclusions: Clinical expression is extremely variable, making it difficult to diagnose. An early diagnosis is important to offer multidisciplinary care and a proper clinical follow-up. Genetic study should be extended to parents to offer genetic counseling. More frequent in our clinical manifestations are characteristic facial dysmorphisms, learning difficulties and heart disease.

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Dietary intake of Australian children with type 1 diabetes exceeds recommendations for energy intake, total sugar and saturated fat

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Background: Healthy diet is essential in the treatment of type 1 diabetes (T1D). Data from USA and Europe suggests that T1D children do not meet dietary guidelines; limited data exists in Australia.
Objective and hypotheses: To evaluate diet in Australian T1D children.
Methods: The Australian Child and Adolescent Eating Survey Food Frequency validated questionnaire was administered to 50 T1D children (aged 14.1±2.1y, 27 males, BMI z-score 1.0±0.62) participating in an RCT (ANZCTR # 126111000148976), to obtain daily macronutrient and energy intake (EI). Daily energy expenditure (EE) and physical activity levels (PAL) were measured with Sensewear. Two age groups were created to enable comparison to data from the 2007 Australian National Children's Nutrition Survey. Australian recommendations and measured PAL were used to estimate energy requirements (ER).
Results: EI exceeded national ER recommendations in all age and gender groups (8-13y: 11380±2542 vs. ER 6467KJ in boys, 11734±29456 vs. ER 5917KJ in girls; 14-18y: 10402±1491 vs. ER 8800KJ in boys, 9917±2006 vs. ER 7140KJ in girls). EI in 8-13 y T1D children was greater than in healthy children of similar age (8922 KJ). Percentage energy from sugar (24±6.4%) and saturated fat (14.1±3.0%) exceeded dietary recommendations (< 20% and < 10%).
8-13y T1D children had significantly higher daily EI, carbohydrate and sugar intake compared to 14-18y (table). There were no differences between the two age groups in gender, protein, fat, PAL (1.2±0.2 vs. 1.2±0.19), or EE (9182±1898KJ vs. 10072±2007KJ).

	8-13 years (n=22)	14-18 years (n=28)	p-value
EI (KJ/day) (mean ± SD)	11524.9 ± 2719.9	10142.3 ± 1802.1	*0.040*
Energy excess (EI-EE)(KJ/day) (mean ± SD)	2341 ± 3189.1	70.3 ± 2230.4	*0.005*
Carbohydrate intake (g/day) (mean ± SD)	344.1 ± 86.6	295.6 ± 53.6	*0.021*
Sugar intake (g/day) (mean ± SD)	176.9 ± 56.7	135.0 ± 47.6	*0.008*

[Baseline Results]

Conclusion: Australian T1D children's diet exceeds recommendations for EI (especially in ages 8-13y), total sugar and saturated fat. Dietary interventions should start early in childhood.

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Characterisation of polyglandular autoimmune syndrome in endocrinology paediatric consult: case reports

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Background: Polyglandular Autoimmune Syndrome is diagnosed when two or more endocrine systems are dysfunctional, along with other non-endocrine immune disorders, specially autoimmune skin diseases.After that, it is necessary an active searching of associations to get the diagnosis of a possible syndrome. These include simultaneous deficiencies in the function of several endocrine glands and other non-endocrine problems.
Objective and hypotheses: To describe the patients with simultaneus polyglandular syndromes and other non-endocrine immune diseases.
Material and methods: A study case series with 73 patients with diagnostic polyglandular syndrome in the consult to Pediatric Endocrinology in the city of Cali Colombia.
Results: Total patients were 73. Female40 (54.7%), male 33 (45.3 %). The clinical manifestations varied greatly and included from two disease components. Diabetes was present in 53 patients (72%), hypothyroidism in 27 (37%), vitiligo in 12 (16%), alopecia in 9 (12%), Juvenile Idiopathic Arthritis (ARJ) in 5 (7%), goiter in 3 (4%), anemia en 2 (2.7%) and candidiasis, polymyositis and dermatomyositis in 1 patient (1.3%). There were multiple endocrine deficiencies associated in these patients.The most frequent association was to total diabetes 20.7% have diabetes and hypothyroidism (11 cases), one with vitiligo.To total de hypothyroidism: 15% have Hypothyroidism and vitiligo (4cases).and 15% ,15% have hypothyroidism and alopecia (4 cases), ARJ and diabetes in 2 cases, hypothyroidism, goiter and vitiligo in 2 cases, hypothyroidism and ARJ in 2 cases, hypotiroidismo, alopecia, vitiligo, dermatomyositis, polymyositis , anemia and ARJ in 1 case. Hypothyroidism, and dermatomyositis in 1 patient with vitiligo.
Conclusions: Several abnormalities endocrine dysfunction may be associated and simultaneously causes various organs in the same patient, the most frequent in this study were diabetes with hypothyroidism, vitiligo and alopecia hypothyroidism.

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Vitamin D status in new onset type 1 diabetes

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Background: Recent studies from Europe and America, suggest that low plasma vitamin D may be involved in the pathogenesis of type 1 diabetes (T1D). Vitamin D is thought to have both direct and indirect effects on various mechanisms related to pathophysiology of diabetes, including pancreatic cell dysfunction, impaired insulin action and systemic inflammation.
Objective: To assess 25OHD status in a group of patients with newly-onset T1D, comparing it to a group of healthy controls; to evaluate the influence of 25OHD levels on disease presentation.
Methods: Longitudinal retrospective case-control study. Clinical and laboratorial characterization of 34 T1D patients at disease onset. Determination of 25OHD levels in 34 T1D and 14 healthy controls from the same area.
Results: Patients were predominantly male (21/34); median age was 8 years. The majority of patients had inadequate 25OHD levels: insufficiency (21-29ng/ml) (48,5%) and deficiency (≤20ng/ml) (12,1%). Although 25OHD levels were lower in males, as previously reported, the difference was not significant. There was no correlation between 25OHD levels and patient characteristics (age, body mass index), disease presentation (form of presentation, season of the year, HbA1C, C-peptide). Mean levels of 25OHD were lower in patients comparatively to controls (29,9ng/ml vs 44,59ng/ml), but the difference was not statistically significant.
Conclusions: The fact that the majority of patients had inadequate 25OHD levels, even though not significantly different from controls, reinforces that awareness to 25OHD status in T1D patients is essential. We believe that screening for 25OHD insufficiency is mandatory at disease onset, and supplementation is to be considered.

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Genetic markers of autoimmune endocrinopathy in Krasnodar region

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Objective: To examine associations of polymorphic alleles of genes *HLA-DQB1, HLA-DQA1, HLA-DRB* with Diabetes Type 1 (DT1), and also its combination with autoimmune thyroadenitis (AIT), celiac disease (CD) in Krasnodar Region children.
Materials and methods: Study of *HLA* - alleles was performed in 110 probands of Caucasian origin diagnosed with DT1, in 52 CD patients and 100 reference group children.
Results: Studies of Krasnodar Region children population revealed that AIT and DT1 combination was recorded in 17 % DT1 patients. AIT and CD was recorded in 5.6 % DT1 patients, CD and DT1 was recorded in Krasnodar Region DT1 0.3 % patients. In Krasnodar Region DT1 patients most frequently occur the following alleles: DQA1*0301, DQA1*0501, DQB1*0201, DQB1*0302, DRB1*04, DRB1*17 regarded as contributing ($p < 0.05$). Distinctions were obtained for alleles DQA1*0102, DQA1*0103, DQB1*0301, DQB1*0602\8, DRB1*11, DRB1*15 that have protective properties. Association with DT1 for allele *0304 of gene *DQB1* described solely in Russian population was recorded in 4.55 % patients of Krasnodar Region and was not detected in control sample. In children suffering from CD most frequently occurred alleles DQA1*0501 (43.8 %), DQB1*0201 (35.9 %), DQB1*0601 (11.4 %), DRB1*11 (31.3 %), ($p < 0.05$). No high prevalence of *DQ2* and *DQ8 HLA*-genes haplotypes in examined patients as compared to their European prevalence (in more than 90 % patients) in studied CD patients was obtained. High frequency of *DQA1*, *DQB1* and *DRB1* genes alleles with protective DT1 effect in celiac disease patients ensure low DT1 prevalence among CD patients of examined population and vice versa. It was established that *HLA-DQB1* *0305 allele ($p < 0.05$) occurred only in patients with combination of DT1 and AIT.
Conclusion: The characteristics of *HLA* - alleles frequency is established for DT1 and combined pathology what can be used for genetic professional advice.

P2-d1-683 Bone, Growth Plate and Mineral Metabolism 3

Cross-sectional and longitudinal comparison of bone mass and quality determinants in young adults with juvenile systemic lupus erythematosus (JSLE) and juvenile idiopathic arthritis (JIA)

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Background: Few prospective data have been published on the use of pQCT in pts with JIA and JSLE. Moreover, few studies have compared in groups homogenous for age and sex, the parameters of bone status using pQCT.
Objective and hypothesis: To evaluate the prevalence of reduced bone mass and density, using pQCT, in two cohorts homogenous for age and sex of patients with JIA and JSLE.
Population and/or methods: 154 JIA pts (127 F, 27 M, median age 20.3 ± 7.9 yrs: 84 oligoarticular, 33 poly, 10 systemic, 27 enthesitis-arthritis (ERA), and 56 JSLE pts (46 F, 10 M, median age 21.5 ± 6.1 yrs) have been studied. The obtained data have been compared with 2 age-sex matched control groups.
Results: JIA patients do not show any difference in comparison to controls as regard to cortical density (CrtBMD), except for systemic patients ($p < 0.0001$) while JSLE patients have a higher crtBMD than controls and JIA pts ($p < 0.005$). Analyzing bone trabecular density (TrbBMD), all JIA patients with different type onsets (except for ERA), and JSLE patients have significant reduced values than controls, with no differences between JIA and JSLE. In addition, JIA patients show a significant reduced muscle area (muscle CSA) than JSLE and controls ($p < 0.001$). The difference is significant in systemic and polyarticular JIA patients, not in oligoarticular and ERA groups. Conversely, fat area (fat CSA) is significantly increased in both JIA and JSLE patients when compared to controls ($p < 0.001$), with no differences in the 2 groups of patients. Same results are observed evaluating the polar resistance to stress (SSIp).
On longitudinal evaluation, the difference of crtBMD, trbBMD, muscle SCA e fat CSA remained unchanged; in JSLE pts, SSIp is stable in comparison to JIA and controls without any difference among JIA pts and controls.
Conclusions: These data might indicate a different pathogenesis of bone damage in the two entities.

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A new mechanism of reduced efficacy of vitamin D therapy in hypoparathyroidism (HPT)

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Introduction: HPT belongs to the well-known complications of total thyroidectomy performed because of thyroid carcinoma. Many factors can influence replacement treatment efficacy.
Case study: We present a case of a 12-year-old boy with iatrogenic HPT, due to total thyroidectomy performed for previous papillary thyroid carcinoma, who presented several hypocalcemic episodes during treatment for an acute promyelocytic leukemia. Over chemotherapy with all-trans retinoic acid (ATRA) he manifested persistent hypocalcaemia (Ca2+< 7.5 mg/l), despite replacement therapy with calcium and 1,25(OH)2D3, the biologically active form of calciferol. We initially supposed that hypocalcaemia was determined by reduced intestinal absorption of calcium, caused by desquamation of the intestinal mucosa or by the decreased gastric acidity due to therapy with pantoprazole. Against this hypothesis there was the complete absence of signs of malabsorption and the lack of normalization of calcium after stopping pantoprazole and despite calcium dose increase. Only doubling 1,25(OH)2D3 dosage just before and during ATRA therapy we controlled hypocalcemia.The possibility exists that ATRA affects directly the action of 1,25(OH)2D3. Some studies, so far performed only in rats, have shown an antagonistic interaction between retinol and calciferol. However the mechanism by which these 2 vitamins interact remains elusive. One more study in rats has demonstrated an antagonistic interaction between not only retinol, but also ATRA and both calciferol and 1,25(OH)2D3, thus indicating that ATRA was not acting on either the cholecalciferol-25-hydroxylase or the 25-hydroxycalciferol-1-hydroxylase enzyme. This seems to be confirmed by our case.
Conclusion: In this case report for the first time we described a probably antagonistic and dose dependent interaction between ATRA and 1,25(OH)2D3 in humans, previously described only in animals. More studies are needed to demonstrate the mechanism of this interaction.

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Response to vitamin D therapy in obese vs. non-obese children and adolescents

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Background: The prevalence of obesity among children and adolescents has been rapidly increasing in recent decade. Obese subjects are at risk for Vitamin D (Vit D) deficiency.
Objective and hypotheses: To investigate the relation of response to vitamin D therapy with obesity in children and adolescents.
Methods: 69 Healthy, obese [body mass index (BMI) > P 95th for sex and age] and 133 matched non-obese control subjects (BMI: P 5th- 85th for sex and age)

suffered from Vit D deficiency/insufficiency received a single dose of 300000 unit intra-mascular Vit D. Response to the therapy was compared between groups by 25 (OH) D level measurement.
Results: Mean level of 25(OH) D before treatment was 13.5±7.2 and 14.5±7.2 in obese and non-obese children and adolescents, respectively and the difference was not statistically significant. After Vit D administration, mean level of 25(OH) D changed to 29.6±8.6 and 33±8.5 in obese and non-obese children and adolescents, respectively. Response to the therapy was statistically different. (P= 0.007).
Conclusions: A single dose of 300000 unit Vit D administration was inadequate to raise blood levels of 25(OH) D in obese children and adolescents.

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Comparison of bone mineral density in adolescent girls with hypogonadotropic hypogonadism and hypergonadotropic hypogonadism

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Background: Deficiency of sex steroids has a negative impact on the bone mineral content. In studies conducted on postmenopausal women and in some animal studies it has been reported that elevated FSH increases osteoclastic activity, decreases bone mineralization and facilitate postmenopausal osteoporosis.
Objective: To evaluate the bone mineral density of adolescent girls with the diagnosis of hypogonadotropic and hypergonadotropic hypogonadism and to investigate the releation between FSH level and bone mineral density (BMD).
Patients and methods: Study group included 33 adolescent girls with the diagnosis of hypogonadism (14 hypogonadotropic hypogonadism and 19 hypergonadotropic hypogonadism). FSH, LH, estradiol level and BMD (using Dexa) were measured.
Results: There were no statistically significant difference between chronologic age (14.9 ±1.5 vs 14.2 ±1.3, p=0.183) and bone age (10.9±1.6 vs 11.1±1.2, p=0.498) of both group. While, serum FSH (1.0± 0.9 vs 109.1± 51.8, p< 0.0001) and LH (0.2±0.19 vs 21.8±12.1, p< 0.000) levels were higher in patients with hypergonadotropic hypogonadism, estradiol level was in prepubertal levels in both group. There were no statistically significant difference between BMD (L1-L4) of patients with hte diagnosis hypogonadotropic hypogonadism and hypergonadotropic hypogonadism (BMD-z scores (L1-L4) were -3.07±1.63 and -3.37±1.08 respectively, p=0.841). A BMD-z score ≤-2.5 were detected in 9 of 14 patients (64.3%) with hypogonadotropic hypogonadism and 15 of 19 patients (78.9%) with hypergonadotropic hypogonadism (p=0.442). Overall rate of BMD-z score ≤-2.5 was 72.7%. There was no correlation between FSH levels and BMD-z scores (r=-0.035, p=0.846)
Conclusion: BMD-z score was found similar and low in majority of adolescent girls with hypogonadotorpic and hypergonadotropic hypogonadism. FSH level was not found to be releated with osteoporosis.

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Marked phenotypic variability and different response to bisphosphonate treatment in osteogenesis imperfecta type V caused by c.-14C>T mutation in *IFITM5* gene

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Background: Osteogenesis imperfecta (OI) type V is an autosomal dominant bone fragility disorder with unique clinical, radiological and histological features caused by a recurrent c.-14C>T mutation in *IFITM5* gene. Marked interindividual phenotypic variability despite identical causative mutation is present and bisphosphonate treatment has similar effect as in other OI types.
Objective: The possible implication of *IFITM5* gene mutation on clinical and radiological characteristics and implication of selected variants in bisphosphonate metabolism genes on response to bisphosphonate treatment was evaluated.
Methods: Following clinical endocrinological and radiological evaluation, sequencing of *IFITM5* exons, exon-intron boundaries and 5'-UTR and genotyping of variants rs2297480 in farnesyl diphosphate synthase gene (*FDPS*) and rs3840452 in geranylgeranyl diphosphate synthase 1 gene (*GGPS1*) was performed in two patients.
Results: Both individuals had multiple recurrent fractures which developed hypertrophic calluses, in one patient only the long bones in the other several small bones of hands were affected. The calluses persisted for years. One of them had scoliosis, the other kyphoscoliosis, both had ossifications of the interosseous membranes of the forearms. Lumbar spine areal bone mineral density (BMD) z scores before beginning of the bisphosphonate treatment were - 3,59 and - 3,6, with good response in one patients (z - 0,2), but without response in the other (final BMD result z - 3,1).The c.-14C>T *IFITM 5* mutation was detected in both individuals in heterozygous state. Both patients carried major *FDPS* variant rs2297480 and were heterozygous for *GGPS 1* variant rs3840452.
Conclusions: Both OI type V patients have previously described identical disease-causing mutation but marked interindividual phenotypic variability and different response to bisphosphonate treatment. Later could not be explained by analysed variants in genes involved in biphosphonate metabolism.

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25-hydroxyvitamin D (25OHD) and bone formation markers (osteocalcin (OC), under-carboxylated osteocalcin (uOC) and N-terminal propeptide of type 1 procollagen (P1NP)) in adult survivors of childhood cancer

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Background: We have reported hyperinsulinism (HI)/abnormal glucose tolerance (aGT) in 15% of adult survivors of childhood cancer, especially after bone marrow transplantation (BMT). Reports of 25OHD deficiency amongst survivors and evidence that bone formation markers (BFM) OC and uOC may be linked to insulin sensitivity led us to explore this in our study population.
Objectives:
1) Is 25OHD deficiency increased in survivors?
2) Do OC ± uOC correlate with insulin sensitivity independent of other BFM (P1NP)?
Methods: 25OHD, OC, uOC & PINP were measured in 99 (55 male) adult survivors of childhood cancer (18-39yrs), median 19.5years [6.3-33.5] after diagnosis. 25OHD levels were compared to published AusDiab controls (n=1393, age 25-35yrs). Relationships with HI/aGT, overweight/obesity (BMI>25kg/m^2) and abdominal adiposity (AA; waist for height ratio>0.5) were sought. Analyses were adjusted for age and gender.
Results: 25OHD levels were lower in survivors compared with controls irrespective of diagnosis or treatment (men 65.5±26.8 vs 73.9±30.0nmol/L p=0.03, women 52.3±20.5 vs 66.6±26.5nmol/L p< 0.001) with 42.4% survivors vs 20.8% controls deficient (< 50nmol/l; p< 0.001).

Survivors	25OHD nmol/mL	OC ng/mL	uOC ng/mL	P1NP ng/mL
Men/Women	65.5 ±26.8/52.3 ±20.5 p=0.008	29.0 ±13.7/19.5 ±6.7 p<0.001	8.2 ±8.9/3.9 ±2.3 p=0.003	78.6 ±39.0/51.4 ±20.4 p<0.001
W:H ratio >0.5 vs <0.5 (CI95%)	-10.6 (-20.1- -1.1) p=0.03	-4.6 (-9.0- -0.1) p=0.04	-1.5 (-4.4 - 1.3) p=0.3	-11.4 (-23.8- 1.0) p=0.07

[Table 1]

With linear regression AA but not overweight/obesity was associated with lower concentrations of OC and 25OHD, with no independent relationship with HI/aGT. BMT was the only treatment modality associated with lower BFMs (OC p=0.005, uOC p=0.03 and P1NP p=0.007) but not 25OHD.

Conclusions: 25OHD deficiency is common in adult survivors. Relationships demonstrated between BFM and abdominal adiposity rather than HI/aGT suggest a link between fat and bone metabolism, stronger for OC than uOC or P1NP.

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Vitamin D-dependent rickets, type 1A causes disproportioned short stature and increased risk of caesarean section

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Background: Vitamin D-dependent rickets type 1A (VDDR1A) is a rare, autosomal recessive disorder caused by a mutation in *CYP27B1* coding for the enzyme one-alpha-hydroxylase that catalyses the final activating step of 25-hydroxyvitamin D (25(OH)D) to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).
Objective: To assess the skeletal consequences of severe rickets during early childhood caused by VDDR1A.
Methods: A total of 7 adults (one male, two siblings) age range 32 to 61 years with VDDR1A were recruited from a larger study on hereditary rickets. The diagnosis of VDDR1A was established by review of patient records. In addition, analysis of *CYP27B1* was performed. The patients underwent anthropometric measurements and DXA scans of the spine and hip.
Results: All seven patients presented with severe rickets between 0.7 to 2.2 years of age, mean 1.8 years. Prior to 1978, all patients received high doses of cholecalciferol. Thereafter patients received alphacalcidol. All patients showed characteristically low values of $1,25(OH)_2D$ despite normal values of 25(OH)D. In four patients mutations in *CYP27B1* were identified. Final height Z-score was significantly reduced to -2.1 SD (-3.2 to -1.1) (mean (95% CI), $p< 0.01$), stature was disproportioned with an increased sitting height ratio of 2.2 SD (0.6 to 3.7, $p=0.01$) due to a relatively greater decrease of leg length compared pairwise to sitting height, -2.8 SD (-4.1 to -1.5) vs. -1.3 SD (-1.9 to -1.1) (p=0.03). In addition, arm span was significantly decreased, -2.6 SD (-3.5 to -1.8) (p< 0.001). Head circumference was not significantly increased, 0.7 SD (0.1 to 1.3) (p=0.059). Four of six women delivered by caesarean section due to disproportioned pelvis. The bone mineral density of the spine and hip was normal.
Conclusions: Severe rickets during early childhood caused by VDDR1A causes short, disproportionate stature and an increased risk of caesarean section when giving birth.

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The incidence and aetiology of childhood hypercalcaemia

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Background: The aetiology of childhood hypercalcaemia is diverse but there are limited data on the relative incidence of the different conditions.
Aim: To determine the incidence and categorise the different causes of childhood hypercalcaemia.
Method: Laboratory records of a children's hospital were searched for all calcium requests on children(< 17yrs) from 2007-2012. Hypercalcaemia was defined as mild (2.9-3.1mmol/L); moderate (3.2-3.5mmol/L) or severe (>3.5mmol/L) and categorised as transient(1day) or sustained(≥2 consecutive days).
Results: Of 61,380 eligible children, 206(0.33%) were identified as having a serum calcium ≥2.90mmol/L of which 165(0.27%), 25(0.04%),16(0.02%) were defined as mild, moderate or severe respectively. 134/206(65%) children were classified as having sustained hypercalcemia (Table 1).

Age	Endocrine	Renal	Oncological	Cardiac	Sepsis	Other	Total
<28days	1	3	2	11	23	15	55
28days-1yr	2	3	1	10	5	11	32
1-5yr	2	9	5	0	1	4	21
6-12yr	2	7	3	0	3	1	16
13-17yr	2	5	1	2	0	0	10
Total	9	27	12	23	32	31	134

[Aetiologies of hypercalcaemia]

Incidence of sustained hypercalcaemia was highest in neonates(41% of all sustained cases) and was inversely related to age. Sepsis was the commonest single cause(24%), particularly in neonates. In most children (renal, oncological, cardiac), sustained hypercalcaemia was related to treatment. Conditions associated with sustained hypercalcaemia seen by endocrinology included adrenal insufficiency(n,4), familial hypocalciuric hypercalcaemia with a CaSR mutation(2), idiopathic hypercalcaemia(1), subcutaneous fat necrosis(1) and Williams Syndrome(1).
Conclusion: Sustained hypercalcaemia is rare in children and its incidence is highest in neonates. All children with sustained hypercalcaemia where the condition is not associated with their medical treatment require investigation to determine the underlying aetiology.

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Bone health evolution over time in childhood solid cancer survivors

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Background: Much has been written on the negative effect of cancer and its treatment on bone formation in childhood cancer survivors. Most of the studies focus on haematological cancers, and little is known on patients with solid tumours.
Objective: To assess bone health evolution in a group of paediatric solid cancer survivors.
Methods: Patients with solid tumours evaluated at Hôpital Necker for bone health status in 2004-2007 were re-evaluated. A clinical exam was performed, fasting blood and urine samples, bone mineral densitometry (BMD) by DXA (corrected for bone age), and dietary evaluation of daily calcium intake. Low bone density was defined as BMD < -1,5 DS in z-score, very low bone density, as < -2,5 DS in z-score.
Results: 27 patients were included, 48,2% were girls. Mean age was 17,1 years (10,7-24,2), 88,9% had ongoing or complete puberty. Mean time in remission was 7,2 years (5,0-10,6). Tumour type was medulloblastoma (51,9%), other brain tumours (7,4%), bone tumours (33,3%), others (7,4%). Vitamin D deficiency (25OH-vitamin D < 30 ng/ml) was observed in 81,5% of patients; 29,6% had < 20 ng/ml. Calcium intake was deficient in 53,9%. Hypogonadism was present in 37%. BMD for spine was normal in 70,4% and low in 29,6%; BMD for femur was normal in 77,8%, low in 18,5% and very low in 3,7%. No significant difference in BMD was observed in patients with hypogonadism or GH deficiency. No significant difference in BMD was noted between the first and the second evaluation. No patient had osteoporosis according to the International Society for Clinical Densitometry 2007 criteria.

Conclusions: Patients with solid cancers during childhood may have persistently reduced BMD which may be difficult to revert, contrarily to what is observed in haematological cancers. Implication of vitamin D deficiency and low calcium intake should be addressed in future studies.

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Bone mass in children with Marfan syndrome: a longitudinal study

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Background: The Marfan syndrome (MFS), a connective tissue disease due to mutations in the fibrillin-1 gene, is better known for its cardiovascular and ocular features than for its bone metabolic characteristics. Fibrillin-1 modulates bone formation by TGF-β. Fibrillin mutations cause a dysregulation of TGF-β signaling leading to an altered bone morphology, including calcium binding pathways.
Objective and hypotheses: Osteopenia is reported in adult MFS patients. Few data are available in children, and no longitudinal assessments are currently available.
Methods: Bone mineral measurements in three skeletal sites (lumbar spine-L, femoral neck-FN and total femur-F) were performed by DXA (Discovery W- Hologic) in 41 children (19 females and 22 males) with MFS diagnosis. The basal assessments were performed at a mean age of 9.1 (±3.3) years, followed by another one after at least 1 year, at 10.7 (±3.5) years. Adjustments for height were made using height-for-age Z-score. BMD changes were expressed as Z-score between visit 1 and visit 2, standardized per year. Bone turnover markers and vitamin D status were measured at each control.
Results: At the first evaluation, MFS children showed reduced BMD values: HAZ-score BMD < 2 was detected in 24% of patients at L, in 25% at FN and in 15% at F. A further decrease of bone density emerges at the second evaluation: BMD values were < -2 in 29% children at L, in 30% at FN and in 25% at F. Fifty-eight % of children showed low bone mass measurements at L, 50% at FN and 67% at F. Bone fractures increased from 2 up to 7 (17%).
The hormonal data were in the normal range, but 25(OH)D values resulted below the recommended cutoff of 30 ng/mL.
Conclusions: The majority of the patients showed a tendency towards a worsening of BMD values. Prevalence of fractures was above the literature average and quickly increased. Losartan therapy, recently introduced, could contrast the progressive deterioration of bone density through TGF-β inhibition.

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Assessment of bone markers and osteoporosis in thalassemia major

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Background: Thalassemia major (β-TM) is a common cause of skeletal morbidity and increased bone fracture risk in patients. Thalassaemic osteopathy is a multifactorial disorder and limited information exists about bone accrual and mineral density (BMD) in children.
Objective and hypotheses: The aim of this study is investigating some potential biochemical bone markers as possible early predictors of BMD variations in children with β-TM.
Methods: Thirty-eight β-TM and 40 control patients were included to the study. Male/Female ratio was 13/25 and 19/21 in patient group and control group respectively. Thirty -eight children with β-TM were subjected to BMD assessment by dual energy X-ray absorptiometry (DXA). Serum beta-crosslaps (Beta-CT_X), osteoprotegerin (OPG), RANKL, urinary deoxypyridinoline (DPD) and ferritin levels were evaluated and compared between the groups
Results: Serum OPG levels in thalassaemic children were significantly lower than controls ((2.01±0.6 pmol/L versus 2.43±0.5 pmol/L, $p < 0.003$). There were no significant differences between the groups according to the mean DPD, Beta-CTx and RANKL levels. Negative correlation was determined between the ferritin levels and vertebra z-score (p=0.021, r:-0.375). Osteopenia (Z score < -2 SDS) was present in the 36.4% of the thalassaemic patients at the spine and 33.3% at the femur site. There was a negative correlation between age and Z score
Conclusions: This study revealed that majority of thalassemic patients have bone resorption which advance with chronological age. Routine BMD screening with DXA and serum OPG levels are suggested to be sensitive predictors for early bone changes, particularly at the lumbar spine.

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Acrodysostosis with hormone resistance: case report

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Background: PRKAR1A dominant gene mutations have been recently described in patients with Acrodysostosis with hormone resistance (AHR).
Objective and hypotheses: We report the case of a female patient (pt) affected by AHR firstly referred to our Centre for pseudohypoparathyroidism 1a (PHP1a).
Case study: At first evaluation in our centre in 2007 the pt (born at term, small for GA, from uneventful pregnancy from unrelated caucasian parents), age 7 years, showed: hyposomia (< -3 SD), skeletal abnormalities (midface hypoplasia, brachymetacarpia and -tarsia, coxa plana, dysmorphic odontoid process of the 1st cervical vertebra with shrinkage of occipital foramen, delayed eruption of teeth), 2 years advanced bone age, conductive bilateral hypoacusia, mild hypocalcemia and hyperphosphoremia with slightly elevated PTH levels, subclinic hypothyroidism. She was on treatment with calcium and calcitriol for pseudohypoparathyroidism. GNAS-1 gene mutation analysis resulted negative. During follow up the patient showed mild neurosensorial transmission deficiency, hypothyroidism (started l-thyroxine), recurrent otitis media, worsening of bilateral hypoacusia, severe tonsils hypertrophia that led to obstructive apneas, reduced growth velocity, overweight. GH deficiency was diagnosed after 2 pharmacological tests and treatment was started for 2 yrs (from 9 to 11 yrs), without growth velocity improvement. In 2012 for the high diagnostic suspicion of AHR, molecular analysis of the PRKAR1A gene was evaluated, showed the heterozygosis for c.1101C>T (p.Arg368stop) mutation and confirmed the diagnosis.
Conclusions: PHP1a and AHR should be both considered in patients with Albright osteodistrophy with hormone resistance and also PRKAR1A gene mutations analysis should be performed in suspicious pts. To our knowledge this case shows clinical features not yet reported in patient with AHR and seems to confirm the heterogeneity of this disease and different tissues sensibility to cAMP levels.

P2-d2-695 Bone, Growth Plate and Mineral Metabolism 4

Bone mineral density in adolescents with hypogonadism

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Background: Hypogonadism may be associated with impaired peak bone mass achievement, resulting in a higher risk for osteoporosis in adult life.
Objective: The aim of the study was to evaluate bone status in adolescents with hypogonadism or *constitutional delay of growth and puberty (CDGP)* and its relation with body composition and treatment modalities.
Methods: 53 patients with age range of 11-22 years underwent anthropometric (height-HT-SDS, waist circumference-WC) and Dual-X-ray absorbiometry evaluations for total body (TB) without-head and lumbar (L) BMD (g/cm^2,

Z-score), BMC (g) and of TB fat mass (FM, %). Twenty-seven (16F) with *hypogonadotropic hypogonadism (group A); 18 (17F) with hypergonadotropic hypogonadism (group B) and 8 (1F) with CDGP (group C).* Eighteen subjects of group A have *secondary hypogonadism and 9 have idiopathic hypogonadism. Eleven males were treated with* testosterone enantate,14 females with oral and 17 with transdermal estrogens (*TD).*

Results: Patients overall showed a reduction of spine bone parameters. In particular a LBMD < -1 Z-score was present in 100% and < -2 SDS in 26%. Group C displayed lower values of LBMD compared to group A (P=0.06). No significant differences were found for HT-SDS and TB bone parameters between the 3 groups.In group A, females tended to have reduced DXA parameters compared to males including *vertebral area (P< 0.02), BMD TB and BMC TB (P's=0,07).* Patients with i*diopathic hypogonadism* showed increased bone parameters (n.s) compared to patients with *secondary hypogonadism*, although the latter group presented increased TBFM% (P< 0.01) and central adiposity (*P< 0,001*). There was an association between replacement therapies and bone parameters, in particular TD with LBMD (r=0.55), LBMC (r=0.66) and vertebral area (r=0.74).

Conclusions: Defective spine mineral density is very common in adolescents and young adults with hypogonadism or CDGP. Treatment of these conditions is beneficial for bone health.

P2-d2-696 Bone, Growth Plate and Mineral Metabolism 4

Evaluation of nephrocalcinosis and nephrolithiasis in eleven children with X-linked hypophosphataemic rickets confirmed with mutations in *PHEX* gene

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Background: The renal phosphate loss is a factor that predisposes to kidney stones formation. The X-linked Hypophosphatemic Rickets (XLH) is caused by inactivating mutations in the *PHEX* gene and is characterized by hyperphosphaturia, becoming a potential risk group to renal lithiasis and possibly to nephrocalcinosis, mainly, during medical management.

Aim: To characterize the phenotype, with emphasis, to the presence of nephrolithiasis and nephrocalcinosis and to analyze the *PHEX* genotype in 11 children with XLH.

Patients and methods: Eleven children diagnosed with XLH had clinical, laboratorial and radiological evaluations. Noncontrast CT multislice of kidneys and urinary tract was performed for the diagnosis of nephrolithiasis and nephrocalcinosis. PCR amplification and DNA sequencing of the entire *PHEX* coding region were performed to analyze the genotype.

Results: All children had leg deformities after starting deambulation without muscle weakness. Most of them had short stature principally when the treatment was retarded. They presented rickets' radiological signs, besides hypophosphatemia and elevated bone markers, mainly, during childhood and growth spurt, even with appropriate treatment. None of the patients had history of urinary infections or urinary tract malformations, neither they had symptoms related to lithiasis. All of them had hyperphosphaturia, without hypercalciuria, hypocitraturia or renal function impairment. CT showed signs of bilateral nephrocalcinosis in 4 of 11 patients, and no signs of nephrolithiais. The *PHEX* molecular analysis confirmed the XLH diagnosis in all children, identifying eight new mutations.

Conclusion: In our cohort, nephrocalcinosis was a frequent co-morbidity in children with XLH, and it may indicate the requirement of early screening and interventions during treatment.

P2-d2-697 Bone, Growth Plate and Mineral Metabolism 4

High prevalence of overweight and obesity in paediatric patients with severe osteogenesis imperfecta: further injury to bone tissue

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Background: O*steogenesis imperfecta* (OI) is a chronic disease, which in severe forms, evolves with decreased mobility and energy expenditure, predisposing to excessive weight gain.

Objective and hypotheses: To determine the prevalence and age of onset of overweight and obesity in patients with severe OI (types III and IV).

Methods: Retrospective study of the annual BMI of severe OI patients treated with pamidronate (PD) over a period of 6 years. Overweight and obesity were characterized, according to the NCHS, by BMI-Zs of +1.0-2.0 and > +2.0, respectively. Dyslipidemia was characterized by plasma HDL < 45mg/dL and/or triglycerides > 100mg/dL.

Results: Forty patients (55.0% male) were analyzed. OI was diagnosed from birth to 9.1 years of age (mean: 1.97 ± 2.64y) and PD was started at 4.79 ± 4.68 years. Twenty nine patients (72.5%) were diagnosed with overweight or obesity at least once during the 6-year follow-up. The mean age at diagnosis of overweight or obesity was 5.79 ± 3.46 years and BMI-Zs mean was +2.01 ± 0.94. Dyslipidemia was identified in 19 out of 29 obese/overweight patients (65.5%).

Conclusions: During the clinical follow-up of patients with severe forms of OI, we should pay attention to their weight gain in order to prevent overweight and obesity. Overweight and obesity represent, in these patients, further injury to an already compromised bone tissue.

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BMD measured by quantitative ultrasound and biochemical parameters in SGA newborn infants

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Background: Premature osteopenia is an important problem of newborn infants. Little is known about osteopenia in infants with SGA.

Objective and hypotheses: The aim of this study was to investigate the osteopenia in infants with SGA by quantitative USG and biochemical parameters and to compare these values in infants with AGA.

Methods: Between June 2010 and August 2011, 64 infants with SGA and 46 infants with AGA born between 34-42 weeks included in the study. Patients with bone diseases or systemic diseases excluded from the study. Blood sample was taken from the infants within two weeks after delivery to measure Ca^{+2}, PO_4^{-3}, Mg^{+2} and ALP; urinary Pyr and DPyr excretion / creatinine (nmol/mmol creatinine) ratio were calculated from the urine samples. Also bone mineral density was measured as SOS (m/sec) from tibia with quantitative USG. Values were compared between two groups with SPSS 16 software.

Results: Serum Ca^{+2}, PO_4^{-3}, Mg^{+2} levels and alkaline phosphatase activity and mean ratios of urinary Pyr and DPyr per creatinine (nmol/mmol creatinine) (28.1 ± 12.2 vs 32.5 ± 14.8, respectively, p= 0.953) were similar in two groups. Median SOS values measured as m/sec on tibias of newborn infants with SGA and AGA were 3100 (2824-3783) vs 3053 (2865-3242), respectively, $p = 0.607$. There was also no difference for these values when compared between symmetric and asymmetric newborn infants with SGA.

Conclusions: The main finding of this study was that there was no difference for bone mineral density measured by quantitative USG between newborn infants with SGA and AGA according to the bone USG. Quantitative bone USG is an inexpensive and reliable method to scan osteopenia in newborn infants.

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Vitamin D supplementation in pregnancy and its effect on cord blood 25 hydroxycholecalciferol and anthropometry of the newborn

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Background: Vitamin D (D3) deficiency is common in India. We previously showed that minimal doses inadequate to keep maternal and cord 25OHD > 20 ng/ml were sufficient to improve neonatal anthropometry compared to unsupplemented mothers.
Objective and hypotheses: To study the effect of higher doses of D3 supplementation in pregnant women on cord blood 25OH D, newborn anthropometry, and pregnancy related adverse events.
Methods: Pregnant women (n=300) in second trimester were randomized to receive under direct observation oral D3 60,000 IU 8 weekly (group 1) or 4 weekly (group 2) or 400 units D3 daily at home (group 3). All were provided 500 mg elemental calcium twice daily. Groups 1 and 2 got tablets without D3, and group 3 with 200 units D3 per tablet.
Results: Of the 300 women, 125 delivered in our institution. Their mean 25OHD (11.2 ± 6.7 ng/ml) and other parameters were not different from the whole group. Maternal 25OHD in groups 1, 2 and 3 at term (18.3 ± 9.6, 21.9 ± 11.2 and 12.7 ± 8.0 ng/ml) and in cord serum (12.4 ± 7.5, 17.1 ± 7.2, 9.1 ± 6.5 ng/ml) were significantly different ($p < 0.001$ for both, in multiple group comparison). Cord serum 25OHD > 20 ng/ml was achieved only in 6.9%, 38.6% and 7.9% in groups 1, 2 and 3 respectively ($p < 0.001$). Neonatal calcium was not different in the 3 groups. Neonatal anthropometry were not different in the 3 groups, but were significantly better than a concurrent comparison unsupplemented group (n=95). Pregnancy related adverse events were not significantly different in the 3 groups.
Conclusions: Oral D3 in doses of 60000 units 4 or 8 weekly or 400 units daily are ineffective in keeping mean maternal or cord 25OHD > 20 ng/ml. All 3 doses ensure similar neonatal anthropometry.

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Bone markers and indirect measures of body composition and metabolic markers in early childhood

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Background: The role of bone on energy metabolism and the crosstalk between adipose tissue and bone has revealed markers of bone metabolism such as osteocalcin and propeptide of human collagen type 1 (PINP-1) related to insulin sensitivity and body composition in adults. However, little is known about this crosstalk in early childhood.
Objective: To investigate the temporal development of bone markers in relation to indirect metabolic markers such as anthropometry, leptin and adiponectin in early childhood.
Methods: PINP-1, osteocalcin, 25-hydroxyvitamin , IGF-1, adiponectin and leptin were measured in 244 children participating in a population-based longitudinal birth cohort in Sweden. Serum was extracted from cord (C) and at 4, 12 and 36 months of age (M). Anthropometric measures of height, weight and waist circumference (WC) were collected at birth, 4,6,12,18,24 and 36 M.
Results: Serum PINP-1 peaked at 4 M with mean (SD) of 1884 (472) ng/ml compared to 1140 (474), 1123 (255) and 698(165) ng/ml, from C, 12 M and 36 M, respectively ($p < 0.001$). A similar pattern was also seen in osteocalcin, raising from 44 (28) ng/ml from C to 98 (36) ng/ml at 4 M ($p < 0,01$) and then decreasing again. PINP levels from C correlated to osteocalcin from C ($r = 0,40$, $p < 0,001$) and weakly to IGF-1 from C ($r = 0,28$, $p < 0,001$). The correlation between PINP-1 and IGF-1 grew stronger with age ($r = 0, 31$, $p < 0,001$ at 4 M and $r = 0,43$, $p < 0,001$ at 12 M). D-vitamin, leptin and adiponectin did not significantly correlate to levels of bone markers.Leptin correlated with WC, but adiponectin did not (data not shown). There was a weak negative correlations between osteocalcin and WC at 4 M ($r = -0,26$, $p < 0,001$). Other bone markers did not correlate to anthropometric measurements.
Conclusions: PINP-1 and osteocalcin present in similar longitudinal patterns during the first years of life with a clear peak at 4 M, reflecting increased bone turnover during this part of infancy.

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Comparison of calcitonin and pamidronate treatments in children with osteogenesis imperfecta

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Background: The main objective of this study was to compare the treatments of calcitonin and pamidronate by clinical, biochemical, and radiological findings in children with osteogenesis imperfecta for the first time in the literature and evaluate the efficiency of pamidronate treatment.
Methods: A total of 12 patients, aged 41±38 (1-120) months were studied. Patients were divided into two groups. Group 1 was consisted of six patients who had received intranasal calcitonin at a dosage of 4-6 U/kg three times a week before switching to pamidronate treatment. Group 2 was also consisted of six patients who had received only pamidronate infusion at a dosage of 0.5-2 mg/kg every two months.
Results: The most impressive effect of pamidronate treatment was observed in reducing pain and fracture rate. Annual fracture rates decreased from 2.72 ± 0.80 to 0.40 ± 0.70 ($p < 0.05$) in group 1, from 3.50 ± 0.54 to 0.40 ± 0.49 ($p < 0.001$) in group 2, and from 4.50 ± 3.30 to 0.32 ± 0.41 ($p < 0.001$) in total 12 patients. The Z-score of bone mineral density increased from -4.12 ± -0.60 to -3.80 ± -1.0 in calcitonin group ($p > 0.05$), and from -3.08 ± -0.61 to -2.29 ± -0.56 in pamidronate group. The difference between the Z-scores of bone mineral density after calcitonin and pamidronate treatments was statistically significant ($p < 0.05$). The Z-scores of pre (-3.44 ± -0.96) and post (-2.47 ± -0.60) pamidronate treatments of whole 12 patients were significantly different ($p < 0.001$).
Conclusions: Pamidronate was significantly more effective in reducing pain, annual fracture rate, and increasing bone mineral density and mobility than calcitonin without any severe adverse effects even in the neonatal period and severe forms of osteogenesis imperfecta.

P2-d2-702 Bone, Growth Plate and Mineral Metabolism 4

Longitudinal study of the effect of Fok-I gene polymorphism of vitamin D receptor on bone mineral density in young patients with β-thalassaemia major

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Background: Biological actions of vitamin D are mediated by an intracellular receptor (VDR). Several single-nucleotide polymorphisms of VDR have been identified with Fok-I being one of the most extensively studied. The polymorphism is represented by 2 allelic variants (F and f), with the f allele leading to the production of a 3 amino acid longer but considered less functional VDR protein.
Objective and hypotheses: To assess the evolution of bone mineral density (BMD) in young patients with β-thalassaemia major over a period of 2 years and investigate the degree of genetic contribution of Fok-I to that.
Methods: Seventy children and young adults (31 females and 39 males) with β-thalassemia major and a mean decimal age of 23.00 ± 6.40 years (range: 7.40- 32.36 years) at the beginning were recruited for this study. All patients

were genotyped for Fok-I polymorphism, whereas BMD was assessed by Dual X-ray Absorptiometry (DXA) at baseline and 2 years after at two sites: lumbar spine (BMDs) and left proximal femur (femoral neck (BMDf) and total hip (BMDh)). Z-scores were calculated based on normal age- and sex-matched Caucasian population.
Results: There was no deviation of the genotype distribution from the Hardy-Weinberg equilibrium: FF genotype accounted for 44.29%, ff genotype for 12.86% and heterozygosity (Ff) for 42.85%. An increased proportion of patients had decreased BMD Z-scores, particularly in lumbar spine and total hip. Patients being homozygous for the f allele had apparently higher BMD z-scores compared with those carrying the F allele in homo- or heterozygosity, however with a difference that did not reached significance. A significantly deterioration in BMD Z-scores measured at femur was recorded in patients carrying the F allele.
Conclusions: Homozygosity for the f allele of the Fok-I polymorphism of VDR seems to have a protective effect on BMD in patients with beta-thal-assaemia major.

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Acrodysostosis and pseudohypoparathyroidism (PHP-Ia): different diseases with similar clinical symptoms

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Background: PHP-Ia is a syndrome produced by mutations in the GNAS gene, leading to a decrease in the stimulatory G-protein alfa subunit, leading to multi-hormone resistance (mainly, PTH and TSH) and Albright's osteodystrophy phenotype (short stature, nasal hypoplasia, facial dysostosis, short phalanges, shortening of the 4-5th metacarpals). These clinical and biochemical characteristics are similar to another disease having a different genetic origin, called acrodysostosis.
Objective and hypotheses: To study 4 children with bone alterations and high PTH and TSH levels in our Endocrinology Unit, in the last 25 years.
Method: Retrospective review of the clinical records of the patients.
Results: 3 cases were diagnosed with PHP-Ia and 1 case with acrodysostosis. The latter was a 3 and a half year old girl referred for study of her short stature. Personal history: Admitted to Neonatology due to hypoglycemia and IUGR (-2.3 SD), karyotype (46 XX). Normal psychomotor development. Family history: nothing of note. Physical examination: Weight 14.5 kg (p35) and length 91.3 p4 (-1.75 SDS), brachydactylia, and depressed nasal base. Skeletal survey showed: short and coarse hand bones; the rest was normal. Laboratory analyses: PTH 117.2 pg/mL, calcium 10.2 mg/dL, calcium ions 4.8 mg/dL, phosphorus 5.6 mg/dL, TSH 14.13 µUI/mL, and FT4 1.2 ng/dL. L-thyroxine replacement therapy was initiated. After a negative result for GNAS, the genetic study revealed a heterozygous de novo mutation in exon 9 of the PRKAR1A gene, diagnostic for acrodysostosis.
Conclusions:
• The clinical and biochemical similarities between PHP-Ia and acrodysostosis can lead to an incorrect diagnosis. Understanding this entity makes it possible to correctly identify these children, in whom no GNAS mutations are found.
• The mutation in PRKAR1A implies cAMP-dependent protein kinase A resistance, giving rise to congenital bone dysplasia and multi-hormone resistance.

P2-d2-704 Bone, Growth Plate and Mineral Metabolism 4

Successful and uncomplicated treatment of generalised arterial calcification of infancy (GACI) with weekly oral risedronate - a four-year follow-up

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Introduction: Generalized arterial calcification of infancy (GACI) is a rare autosomal recessive (AR) condition characterized by extensive arterial calcification of large and medium-sized arteries which begins in utero. Many affected infants are stillborn or die in infancy. Although some affected individuals have ABCC6 mutations, most have mutations of the ENPP1 gene resulting in nucleotide pyrophosphatase / phosphodiesterase (NPP1) deficiency and decreased inorganic pyrophosphate (PP_i) generation. PP_i is a potent suppressor of hydroxyapatite deposition and inhibits ectopic chondrogenesis and calcification.
Case presentation: This AA/Caucasian girl was seen at 3 months of age for evaluation of possible non-accidental trauma. Radiographic skeletal survey revealed linear ectopic calcification following a vascular pattern. A subsequent CT scan confirmed GACI. Given reports indicating arrest of progression and prolonged survival with bisphosphonates, we started risedronate 1mg/kg once weekly at 3.5 months of age. Her electrolytes, including calcium, phosphate, vitamin D 25OH, parathyroid hormone (PTH), urinary calcium were normal initially and have remained so. Renal and cardiac assessments were done prior to and during risedronate therapy to monitor the disease advancement. Serial CT angiograms and cardiac evaluations have shown no progression of coronary calcification. Follow up renal ultrasound and CT scan at four years of age revealed minimal to no progression and no arterial stenosis. Her growth and development have been normal. She has not developed rickets, hypophosphatemia, or joint calcification.
Conclusion: GACI is a very uncommon AR disease which can be disabling or fatal early in life. After four years of weekly oral risedronate our patient is doing remarkably well, with no demonstrable progression of the disease, normal growth and development and no adverse effects related to the treatment.

P2-d2-705 Bone, Growth Plate and Mineral Metabolism 4

Case report: juvenile Paget's disease in an Iranian kindred with vitamin D deficiency and novel homozygous TNFRSF11B mutation

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Background: Juvenile Paget's disease (JPD) is a rare heritable osteopathy characterized biochemically by markedly increased serum alkalinephosphatase (ALP) activity emanating from generalized acceleration of skeletal turnover. Affected infants and children typically suffer bone pain and fractures and deformities,become deaf, and have macrocranium.Some who survive to young adult lifedevelop blindnessfrom retinopathyengendered by vascular microcalcification. Most cases of JPD are caused by osteoprotegerin (OPG) deficiency due tohomozygous loss-of-function mutations within the TNFRSF11B gene that encodes OPG.
Objective and hypotheses: Reporting a new mutation with a new presentation of juvenile paget disease.
Methods: We report a 3-year-old Iranian girl with JPD and craniosynostosis who had vitamin D deficiency and hyperphosphatasemia together with low-normal calcium and low inorganic phosphate and 25-hydroxyvitamin D levels. Several family members in previous generations of this consanguineous kindred may also have had JPD and vitamin Ddeficiency.
Results: Mutation analysis showed homozygosity for a unique missense change (c.130T>C, p.Cys44Arg) inTNFRSF11B that would compromise the cysteine-rich domain of OPG that binds receptor activator of NF-κB ligand (RANKL). Both parents were heterozygous for this mutation. The patient's serum OPGlevel was extremely low and RANKL level markedly elevated.

She responded well to rapid oral vitamin D repletion followed by pamidronate treatment given intravenously.
Conclusions: Our patient is the first Iranian reported with JPD. Her novel mutation in TNFRSF11B together with vitamin D deficiency in infancy was associated with severe JPD uniquely complicated by craniosynostosis. Vitamin D repletion followed by pamidronate treatment can be effective for the skeletal disease caused by the OPG deficiency form of JPD.

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Decreased vitamin D levels in children with familial Mediterranean fever

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Objectives: To determine the frequency of vitamin D deficiency in children with familial Mediterranean fever (FMF) and to investigate the factors associated with low vitamin D status.
Methods: Forty-four patients with FMF and 39 age- and sex-matched healthy controls were enrolled in this study. Demographic data, disease duration, time to delay for diagnosis, FMF symptoms, disease severity score, MEFV mutation, dose and duration of colchicine therapy and compliance to treatment were recorded for each patient. Serum 25- hydroxyvitamin D levels were measured by original commercial kit based on Chemiluminescent Microparticle İmmunoassay (CMIA) principle.
Results: The serum 25- hydroxyvitamin D levels were significantly lower in FMF patients than the healthy controls (12.9 ± 3.6 and 16.3 ± 5.5, respectively, p=0.001) The vitamin D level was similar in patients homozygous for M694V and other genotypes (11.8 ± 3.7 and 13.2 ± 3.6, respectively, p=0.21). There was a significant negative correlation between the duration and cumulative dose of colchicine use and vitamin D levels (r=-0.410, p=0.006 and r=-443, p=0.004, respectively). There was no correlation between vitamin D levels and current dose of colchicine, CRP, WBC, disease duration, disease severity score or age of the patient.
Conclusion: Our results suggest that serum 25- hydroxyvitamin D levels are decreased in children with FMF. Duration of colchicine use and cumulative colchicine dose appear to affect vitamin D levels negatively.

P2-d3-707 Bone, Growth Plate and Mineral Metabolism 5

Does medication use during pregnancy in patients with rheumatoid arthritis (RA), influence bone density of children aged 5-8 years?

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Background: Medication use in pregnant women with rheumatoid arthritis (RA) is restricted to prednisone, sulfasalazine, or hydroxychloroquine. Prednisone can lead to low 25-hydroxyvitamin D (25-OH-D_3) serum levels which can lead to low bone mineral density (BMD) of the mother and even of the child until 8 year of age. Other studies showed that sulfasalazine is positively correlated with high BMD in patients with RA.
Objective: Does medication use during pregnancy influence the bone mineral density in children (age 5-8) of mothers with RA?
Methods: Children of mothers who participated in the PARA-study, a prospective, nationwide cohort study on RA during pregnancy. Dependent variables: Birth weight SDS (standard deviation score); BMD_{TB}SDS (total body), BMD_{LS}SDS (lumbar spine), $BMAD_{LS}$SDS (Bone Mineral Apparent Density), Body Mass Index SDS (BMI) at the age of 5-8 years; Independent variables: medication (prednisone; sulfasalazine, hydroxychloroquine) during pregnancy; current 25-OH-D_3 level of the child.
Results: Of 108 children studied the mean birth weight SDS was 0.03 (1.13); BMD_{TB}SDS was -0.11 (0.10); BMD_{LS}SDS was -0.20 (0.99); $BMAD_{LS}$SDS was -0.05 (1.03); BMI SDS was 0.01 (1.13). There was correlation between birth weight SDS and BMD_{TB}SDS (r= 0.23, p< 0.01); BMD_{LS}SDS (r= 0.22, p< 0.01) and BMI SDS (r=0.30, p< 0.0001). There was a positive association between sulfasalazine use during pregnancy and BMD_{TB}SDS of the child (r=0.55; p< 0.01) and no association between maternal prednisone or hydroxychloroquine use and BMD. Correcting for RA disease activity did not influence these associations. The mean 25-OH-D_3 level of the child was 65.99 nmol/L (18.30). There was no correlation between 25-OH-D_3 and BMD.
Conclusions: Children born from mothers with RA have a normal bone mineral density at the age of 5-8 years. Prednisone use during pregnancy has no correlation with the BMD, but sulfasalazine could have a positive effect on the BMD_{TB} of the child.

P2-d3-708 Bone, Growth Plate and Mineral Metabolism 5

GH-induced short term changes of serum bone markers in children with idiopathic short stature

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Background: GH therapy is known to accelerate bone remodelling and collagen turnover in children with idiopathic short stature (ISS). The short term changes in serum bone markers following GH administration in relation to stature and adiposity have not been evaluated in ISS children.
Objective and hypotheses: The changes in serum bone markers were investigated after one week of GH administration and their relationship with the degree of height deficit, adiposity and short term increments in IGF-1 and IGF BP3 were investigated.
Methods: In addition to IGF-1 and IGF-BP3, bone-specific alkaline phosphatase (BALP) and C-terminal telopeptide region of type 1 collagen (CTX) were measured by commercial immunoassays during an IGF-1 and IGF-BP3 generation test (Nutropin 0.05mg/kg.day for 7 days) in 13 prepubertal ISS children with a low circulating IGF-1 and a normal GH reserve.
Results: Serum IGF-1 increased with more than 30 microg/L in all but one subject and serum IGF-BP3 increased with more than 0.6 mg/L in all after one week of GH administration. Whereas median serum BALP did not change significantly (median (range) increase of -6 (-100 to 24) %, serum CTX increased significantly (p< 0.005) from 1.29(0.61) to 1.86(3.6) microg/L (= increase of 15 (-6 to 1633) %). The absolute increase as well as the relative (in terms of percentage from baseline) increase in serum CTX correlated positively with basal serum leptin (r= 0.57 and 0.53, p< 0.05). Neither the absolute, nor the relative changes in serum CTX correlated with the age, the height deficit, the basal values or increments of serum IGF-1 and IGF-BP3.
Conclusions: The short term increase of serum cross-links to high dose GH administration varies between ISS subjects, is influenced by the basal leptin concentration and is independent of the IGF-1 generation. The value of short term increments in CTX (in relation to leptin) for predicting the responsiveness to GH in ISS children needs further study.

P2-d3-709 Bone, Growth Plate and Mineral Metabolism 5

Does disease treatment influence bone mineral density in children and adolescents with inflammatory bowel disease?

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Background: Bone loss is now receiving increased attention as a complication of inflammatory bowel diseases (IBD) in children and adolescents. Objective and hypothesis. To evaluate the effect of different treatments in-

cluding enteral nutrition on bone loss, and to identify risk factors in pediatric patients with Crohn's disease (CD) and ulcerative colitis (UC).
Population and/or methods: We evaluated 62 patients (median age 14.1 years; 29 UC, 33 CD). Bone Mineral Apparent Density (BMAD) at lumbar spine by dual energy X-ray absorptiometry (DXA) and biochemical bone markers were assessed. Therapy with infliximab, azathioprine, 6-mercaptopurine (AZA/6-MP), corticosteroid and enteral nutrition was considered.
Results: Prevalence of low BMAD (Z-score ≤ -2) was 29%. No significant differences between CD and UC were found. Small bowel involvement resulted to be a risk factor in CD. In CD patients, both enteral nutrition and infliximab therapy showed a significant positive effect on BMAD. Multivariate analysis of variance showed significant positive effect of steroid treatment on BMAD and a negative effect of AZA/6MP. No correlations with biochemical markers were found.
Conclusions: Many children with IBD have a low BMAD. Small bowel CD is a risk factor. Nutritional therapy and infliximab have positive effect on bone status.

P2-d3-710 Bone, Growth Plate and Mineral Metabolism 5

Increased serum interferon-γ (IFNγ) concentration is positively associated with increased total body bone mineral content and density in 10- to 11-year-old overweight boys

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Background: Adipose tissue has been metabolically linked to bone. Different markers of inflammation are associated with obesity and may influence bone health.
Objective and hypotheses: To investigate associations of serum levels of 13 biochemical inflammatory markers with total body (TB) and lumbar spine (LS) bone mineral values in overweight boys**.**
Methods: 38 boys with normal BMI (NWB) and 38 boys with BMI > 85th percentile (OWB) at the age of 10-11 years participated in this study. Measurements included serum concentrations of IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFNγ, TNF-α, IL-1α, IL-1β, MCP-1, EGF and CRP; TB and LS bone mineral content (BMC) and bone mineral density (BMD) and body composition values. High-sensitive chips were used to measure 13 markers of inflammation, while body fat mass (FM), fat free mass (FFM), BMC and BMD were assessed by DEXA. Bone mineral apparent density (BMAD) was also calculated for the TB and LS.
Results: Mean TB BMD, LS BMD, TB BMC and BMC/height in OWB were significantly higher (all $p < 0.05$) and mean TB BMAD significantly lower than in NWB (0.085 ±0.007 vs 0.093±0.004 g/cm3, $p < 0.05$), whereas mean LS BMAD did not differ between the groups. Out of the 13 measured biochemical parameters, serum IFNγ concentration was positively correlated with TB BMD ($r=0.36$; $p< 0.05$), TB BMC ($r=0.38$; $p< 0.05$) and BMC/height ($r=0.53$; $p< 0.01$) in OWB group whereas no significant correlations were found in NWB group. In OWB serum IFNγ level explained 25.0% of the variability in BMC/height. In NWB group, serum IL-1α level was inversely related to TB BMC ($r=-0.37$; $p< 0.05$) and EGF positively to LS BMAD ($r=0.32$; $p< 0.05$).
Conclusions: Overweight boys have greater total body BMD and BMC, but lower BMAD than NWB. The effect of excessive fat mass on bone mineral characteristics may be mediated by IFNγ.

P2-d3-711 Bone, Growth Plate and Mineral Metabolism 5

Management of a new case of neonatal hypocalciuric hypercalcaemia related to mutation of the calcium-sensing receptor gene with bone abnormalities

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Case study: A 5-month-old girl was referred to our bone unit after a systemic neonatal screening for hip luxation by x-rays revealed bilateral femoral bowing.
She was the first child of healthy non-consanguineous parents, and her family history was unremarkable. Her parents had a normal physical examination, and normal laboratory findings.
At presentation, her height was 64.0 cm (Z-score: 0.0) with a regular height velocity. Weight was 7.4 kg (Z-score: 1.0). On physical examination, there was bilateral bowing of the femurs. The remaining examination was unremarkable.
A skeletal survey revealed bilateral femoral bowing without other bone abnormalities.
Laboratory investigations revealed mild hypercalcemia (total calcium 3.20 mmol/l), normal phosphatemia (phosphate 1.6 mmol/l), normal serum alkaline phosphatase (alkaline phosphatase 643 UI/l), an inappropriate elevated serum level of intact PTH (85 pg/ml), and normal urinary calcium/creatinine ratio (0.42 mmol/mmol). Serum 25-hydroxyvitamin D_3 ($25OHD_3$) level was normal (23 ng/ml).
Calcium-Sensing Receptor (CaSR) gene analysis found combined heterozygote mutations with a missense mutation resulting in amino-acid N592S substitution in the extracellular domain and a R648X nonsense mutation.
Evolution: Intravenous disodium pamidronate (2 infusions of 0.5 mg/kg and 1.0 mg/kg at months 6 and 7 respectively) was administrated to control the excess of bone resorption and hypercalcemia. Tolerance was good. Calciuria decreased under treatment. Cholecalciferol was associated.
Conclusion: We report here a new case of neonatal hypocalciuric hypercalcemia responsible for bone deformity with combined mutations of the CaSR gene. Because of the bone presentation, we indicated bisphosphonate treatment in order to reduce hypercalcemia and the consequences of chronic hyperparathyroidism. Calcemia remained controlled and calciuria was reduced, indicating reduction of bone turn-over.

P2-d3-712 Bone, Growth Plate and Mineral Metabolism 5

A novel cytoplasmatic mutation of the calcium-sensing receptor (CASR) in a newborn resulting in familial hypocalciuric hypercalcaemia (FHH)

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Background: The calcium-sensing receptor (CASR) is a member of the G protein coupled receptor family expressed in the parathyroid gland and kidney tubule. Inactivating CSAR mutations result in familial hypocalciuric hypercalcemia (FHH). All known CASR mutations are located in the extracellular and transmembranous domains of the receptor.
Case report: A male term-eutrophic newborn presented at the 3rd day of life with petechiae, thrombopenia (22 GPt/l, NR 150-400) and a mild hypercalcemia of 1.5 mmol/l (NR 1.0-1.2). In addition the boy showed severe but transient hyperparathyroidism (maximum 389 pg/ml; NR 11-67), low phosphate (P) level of 0.9 mmol/l (NR: 1.3-2.5), reduced urine Ca/creatinine (Crea) and P/Crea ratios and a rising hypercalcemia with a maximum of 3.1 mmol/l. Phosphate substitution was started at day 5 and vitamin D (500 E/d) was given starting at an age of 8 days. In the further course the breastfed infant developed a sucking weakness, repeated vomiting and muscular hypotonia. He was dismissed after 14 days still receiving oral P substitution.

Sequencing of the *CASR* revealed a CGG>CCG transition resulting in an inactivating heterozygous p.R886P mutation. Arginine 886 belongs to the cytoplasmic domain of the receptor and is highly conserved between species. The parents were tested negative for this mutation indicating that it occurred spontaneously.
After one platelet concentrate transfusion thrombopenia resolved. Neonatal alloimmune thrombopenia (NAIT) was assumed because of characteristics findings in the HPA typing of the parents.
Conclusion: The reported mutation p.R886P is the first detected intracellular mutation of the *CASR* causing FHH. Simonds et al. identified the same mutation in a patient suffering from isolated normocalciuric hyperparathyroidism but no thrombocytopenia.
This is therefore the first report of a FHH patient with a proven *CASR* mutation and neonatal thrombopenia. A potential association between the two conditions remains elusive.

P2-d3-713 Bone, Growth Plate and Mineral Metabolism 5

Kearns-Sayre syndrome presenting with hypoparathyroidism in a child

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Introduction: Kearns-Sayre Syndrome (KSS) is a rare multisystem mitochondrial disorder caused by deletions in mitochondrial DNA gene. It is characterized by progressive external ophthalmoplegia, pigmentary retinopathy and conductive cardiac defects. Here we report a patient with Kearns-Sayre Syndrome presented with hypoparathyroidism.
Case study: An 11 year old girl presented with progressive ptosis, ophthalmoplegia and short stature noted at the age of 3 years. She was born at term with birth weight of 3.5 kg and she went through normal development. Parents are consanguineous with no family history of metabolic or endocrine disorders. She was admitted at the age of 8 years with carpopedal spasm and discovered to have severe hypocalcaemia responded to intravenous calcium and One alpha Calcidol. Examination showed height of 118 cm, less than 3rd centile. Eye examination indicated bilateral ptosis, external ophthalmoplegia and pigmentary retina. Laboratory investigations showed PTH level of 0.22 PM/L (N=1.65-6.9) . Lactate, serum amino acid, urinary organic acid, alkaline phosphatase, Vitamin D profile, thyroid function and growth hormone stimulation test were normal. Muscle biopsy confirmed presence of ragged fibers. COX was pale in scattered fibers. Electron microscopy revealed enlarged pleomorphic mitochondriae and others showing lamellated cristae with concentric profiles or dense inclusions consistent with mitochondrial myopathy. MRI brain revealed bilateral symmetrical abnormal high T2 signal intensity involving globus pallidi, thalami and the posterior aspect of the midbrain, pons and medulla with increase lactate peak on MR spectroscopy.
DNA testing for KSS revealed a known disease causing mutation.
Conclusions: This report highlights the important association of hypoparathyridism and Kearns-Sayre syndrome. This should be considered in all patients with mitochondrial disease especially KSS who presented with hypocalemia.

P2-d3-714 Bone, Growth Plate and Mineral Metabolism 5

The effect of vitamin D on childhood migraine attacks

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Background: Migraine in childhood is a cause of frequent, chronic, progressive and repeating headache. While a large number of drugs can be used for acute and prophylactic treatment in adults, the number of specific agents in pediatric patients is inadequate, and the use of alternative therapies is widespread.
Objective and hypotheses: The objective of this trial is to evaluate serum vitamin D levels in cases with childhood migraine and to investigate the effect of vitamin D therapy on attack frequency in migraine.
Methods: A total of 53 children diagnosed with migraine were enrolled as the Study Group. A total of 69 children with similar demographic characteristics were enrolled as the Control Group. Calcium, phosphorus, alkaline phosphatase parathormone and 25 OH vitamin D levels were measured. Patients were classified into groups on the basis of their vitamin D levels. Vitamin D in addition to anti-migraine treatment was given based on vitamin D levels. No vitamin D was given to the group with normal 25 OHD levels. Patients were observed for six months, and attack numbers were recorded. The trial was approved by local ethics committee.
Results: Comparison of serum 25(OH) vitamin D levels in Study and Control groups revealed a statistically significant difference ($p < 0.05$). Comparison of the vitamin D groups with the group receiving no vitamin D in addition to anti-migraine treatment revealed a significant difference in attack frequency.
Conclusions: Vitamin D given in addition to anti-migraine treatment exhibits a positive effect on childhood migraine attacks. We think there may be a relationship between vitamin D and migraine.

P2-d3-715 Bone, Growth Plate and Mineral Metabolism 5

Short stature, osteoporosis and fractures are not always due to osteogenesis imperfecta: two cases diagnosed with lysinuric protein intolerance

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Background: Lysinuric protein intolerance (LPI) is a rare inborn metabolic disease presents with variable findings including different organ systems.
Objective: To report two cases of LPI who presented with short stature and osteoporosis, and to emphasize the importance of screening inborn errors of metabolic diseases in patients with such symptoms.
Results: The first case, an 8 year old boy presented with several bone fractures and carried the diagnosis of osteogenesis imperfecta (OI). On presentation to our clinic, he had severe growth failure (height SDS of -3.2), abdominal distension and muscle atrophies. On laboratory, IGF-I level was under the detection limit with normal peak growth hormone (GH) levels on stimulation test. He also had microcytic anemia with elevated ferritin and lactate dehydrogenase. Bone mineral density (BMD) z-score was -3.67. On X-ray, severe osteoporosis with severe platyspondily and compression fractures of vertebrae had been detected. The history of protein-rich food refusal lead to metabolic screening which showed increased urinary lysine and ornithine with decreased plasma lysine diagnostic for LPI. The second case, a 13 year old boy presented with short stature. Height SDS was -5.1. He also had fractures three times involving long bones. The midfacial hypoplasia, pallor, deformity of the extremities were detected on examination. On laboratory, anemia with elevated ferritin, normal peak GH levels had been detected. BMD z-score was -4.60. Urine and plasma screening showed elevated urine lysine with decreased plasma lysine levels again diagnostic for LPI. Hyperammonemia were not detected in cases due to the aversion to protein-rich food, however, both patients had elevated plasma glutamine levels.
Conclusions: Short stature and osteoporosis/fractures are the common problems in LPI, which can be presented to Pediatric Endocrinology clinics and be misdiagnosed as OI. Metabolic screening should be considered in such cases.

P2-d3-716 Bone, Growth Plate and Mineral Metabolism 5

A novel de novo activating mutation of calcium-sensing receptor (CaSR) in a patient with hypocalcemia and long QT syndrome (LQTS)

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Background: CaSR, mainly expressed in the parathyroid gland and kidney, is activated by extracellular calcium (Ca) concentration, triggering inhibition of PTH secretion and decreased renal Ca reabsorption. Autosomal dominant hypocalcemia (ADH) is caused by CaSR activating mutations and its clinical manifestations range from severe neonatal hypocalcemia to mild signs incidentally found in adults. Clinical hallmarks are hypocalcemia, hyperphosphatemia, hypercalciuria, and inappropriate levels of PTH.
Case report: A 7-year-old boy, under β-blocker therapy for an asymptomatic LQTS diagnosed at 2 months of life, with negative genetic investigation, was referred to us because of hypocalcemia. Inappropriately low/normal PTH, hyperphosphataemia, and hypercalciuria were present; cerebral CT detected basal ganglia calcifications; nephrocalcinosis was absent. Ca concentration was normal in both parents. Patient was treated with calcium carbonate and calcitriol, associated with thiazide. In spite of a short, therapy-induced, period of normocalcemia, QT prolongation improved only slightly and hypercalciuria remained. To avoid nephrocalcinosis, supplement therapy was stopped, only the β-blocker was continued.
Methods: DNA was extracted from venous blood samples. The *CaSR* gene-coding and flanking regions were PCR amplified. Nucleotide sequences of the PCR products were determined using automated sequencer and compared with reference sequence in the Ensembl database.
Results: Molecular analysis of the *CaSR* gene revealed a novel heterozygous deletion (c.2682delC), determining the substitution of serine with proline in position 895 (p.S895P fs*44), responsible for a frameshift leading to a premature stop codon. The mutated protein lacks of the C-terminal portion, determining an incomplete intracellular domain.
Conclusions: This is the first report on the association between ADH and LQTS. In our patient we observed only a slight improvement of LQTS during therapy-induced normocalcemia.

P2-d3-717 Bone, Growth Plate and Mineral Metabolism 5

Different phenotypes associated with inactivating mutations of the GNAS gene

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Introduction: GNAS gene encodes the α-subunit of the G protein. Heterozygous inactivating mutations in GNAS gene (20q13.2) have been associated with variable phenotypes including pseudohypoparathyroidism, Albright hereditary osteodystrophy, progressive osseous heteroplasia and osteoma cutis. GNAS gene is subject to complex imprinting control.
Case report: We report 2 cases of GNAS gene inactivating mutations.
Case1: Female. IUGR diagnosed at 28 weeks. Induced delivery at 37 weeks.Apgar:8/9. Resuscitation no required.W:1800gr (-2.42SD), H:43 cm (-2.45SD), HC:31.5 cm (2.32SD). Phenotype:mild facial dysmorphia. Admission to neonatal unit due to early hypoglycemia. First month: transient TSH elevation. At 7 months of age erythematous/violet skin lesions appeared in buttocks, several in left gluteal region, with underlying induration areas. Biopsy:plate-like osteoma cutis.Serial bone and Ca/P metabolism: normal. PTH:79pg/ml.
Genetic study: Mutation in exon 12, consisting c.1036delC; p.Leu346X.
Case 2: Male. Mother:hemolytic anemia, hypothyroidism treated and cutaneous calcinosis. Prenatal ultrasound (36 weeks): macroglossia, short bones and right hydronephrosis grade III. Caesarean section at 41.6 weeks, Apgar:6/9. Resuscitation with ambu-bag.W:3320gr (-0.8SD), H:49cm (-1.3SD), HC:37cm (0.95SD). Phenotype: limit set ears, tongue protrusion, small nuchal translucency and bilateral simian crease. Admission to neonatal unit due to early hypoglycemia and respiratory distress. Hypothyroidism diagnosed at third day of life (TSH:50.4μIU/ml, FT4:0.96ng/ml, Ab:285 IU/ml). Treated with L-thyroxine.
Evolution: Diuretic renogram with left renal obstructive pattern, operated at 3 months. At 6.5 month: skin calcifications.Biopsy: osteoma cutis. Ca/P metabolism: normal. PTH:103pg/ml. Treatment: calcium, vitamin D, calcitriol and low phosphate diet.
Genetic study: Mutation in exon 7, consisting c.565_568delGACT; p.Aspl89fs.
Conclusions: We report two heterozygous inactivating mutations in GNAS gene (20q13.2) associated with two different phenotypes.

P2-d3-718 Bone, Growth Plate and Mineral Metabolism 5

Bone health determinants in spinal muscular atrophy

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Background: Osteopenia and fractures are reported in spinal muscular atrophy (SMA).
Objective and hypotheses: Aim of our study was to evaluate determinants of bone status in SMA patients.
Methods: DXA measures of total body less head bone mineral density (TB-BMD,g/cm^2 and Z-score), bone mineral content (TB-BMC, g), fat mass (FM%, kg) and fat free mass (FFM kg) were obtained in 17SMA subjects; 14 patients (n=9 SMAII, 4F, 5M; n=5 SMAIII, 4F, 1M) and 19 controls (9F and 10M) < 20 yrs of age were analyzed at T0 (9,6±4,0 yrs), T12 and T24 months. Patients underwent height (HT SDS), body mass index (BMI SDS), FMI (FM, kg/m^2) evaluations. Five subjects (n=3M with SMAII, and 1F and 1M with SMAIII) reported fragility fractures.
Results: SMAII and SMAIII subjects did not differ for age, HT SDS, BMI, FM, FFM and FMI although SMAII tended to be shorter and to have less FFM than SMAIII subjects at all time points. Controls were significantly taller compared to both SMA groups.
TB-BMC and BMD-Z-score values were significantly reduced in SMAII compared to SMAIII and controls at all time points, while they were not significantly different between SMAIII patients and controls. Controls, SMAII and SMAIII showed a significant increase of BMD over 2 years (0,082g/cm^2, P< 0,001; 0,038g/cm^2, P=0.03 and 0,116g/cm^2, P=0.01, respectively), with an absolute TB-BMC increase of 260g, 75.4g and 96,3g during the observation period. TB-BMD Z-score was inversely related to age in SMAII subjects and fell below normal values for age and sex (< -2 Z-score) in 70% of them by 15 yrs of age. DXA parameters did not discriminate between fractured and not fractured SMA patients. In contrast BMI, FM and FMI were significantly higher and FFM significantly reduced in SMAII subjects with fractures compared to SMAII without bone events (Ps< 0,05).
Conclusions: SMAII patients present a profoundly compromised bone status; body composition may be a major determinant of their skeletal fragility.

P2-d1-719 Bone, Growth Plate and Mineral Metabolism 6

Is anaemia and neutropenia always associated with primary disease in hereditary bone marrow syndrome? Myelofibrosis associated with vitamin D deficiency

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Rickets is a disease of growing child.We report two cases of inherited bone marrow failure syndrome to emphasize effect of Vitamin D deficieny on hematological parameters.The first patient having cartilage-hair hypoplasia presented with convulsion.He was 6 year-old-male. His height was disproportionate and he'd short-limbed dwarfism, hepatosplenomegaly, thin and sparse

hair, rachitic rosaries, widened wrists, and ankles. Hb level was 8.4 g/dl, WBC 2.5*109/L and PLT 7*109/L.Serum calcium was 3.5 mg/dl, phosphorus 2.7 mg/dl, alkaline phosphatases 750U/L, parathormone level 275.4 pg/ml, 25-OHD3level < 5 ng/ml.Vitamin D, calcium lactate was administered. Biochemical abnormalities returned to normal level and there was a significant improvement in hemotological parameters The second patient having Schwachman-Diamond syndrome presented with carpopedal spazm. He was 3 year-old-male. His weight and height were below the third percentile. Hb level was 7.2 g/dl, WBC 1.09* 109/L and PLT 3,41*109/L. Serum calcium was 5.2 mg/dl, phosphorus 2.0 mg/dl with alkaline phosphatase 1000 U/l ,serum 25-OHD3 level was< 5 ng/ml, parathormone level was 354 pg/ml.VitaminD, calcium lactate was subsituted.At follow up, patients's biochemical abnormalities was corrrected with the vitamin D therapy. Hematological values were improved .Gradual improvement in hematological parameters of these patients led us the diagnosis of myelofibrosis attributed to vitamin D deficiency. Myelofibrosis associated with rickets is a rare complication. it can be reversed with Vitamin D therapy.It is important that patients who are frequently hospitalized, little sunlight exposure or isolated because of infection risk are at greater risk of vitamin D deficiency. Because of increased risk of deficiency, monitoring 25 hydroxy vitamin D status especially in winter months and Vitamin D supplementation have to be highly recommended to prevent vitaminD deficiency in these patient group.

P2-d1-720 Bone, Growth Plate and Mineral Metabolism 6

Risk of over the counter vitamin D supplements: a case of unintentional chronic vitamin D intoxication of an infant

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Background: Infants who drink < 1L VitaminD (VD) fortified formula should receive 400IU of VD daily per AAP Guidelines. Use of over-the-counter(OTC) supplements has led to cases of VD intoxication (VDI) with serious renal, cardiac and neurologic effects.
Objective: We present an infant exposed to chronic unintentional VD overdose, highlighting potential danger of concentrated vitamin supplements in children.
Methods: Case presentation and review of literature.
Case: A 6 month old, previously healthy Caucasian female was referred to emergency care for poor weight gain (birth weight 4.5kg, 7.2kg at 2months, and 7.5kg at 6months), fussiness, and constipation for 6weeks. Medical / social histories were negative. Physical examination was unremarkable.
Screening laboratory tests showed sodium 129meq/L, calcium 20.2mg/dL, phosphorus 3.1mg/dL, magnesium 1.9mg/dL, BUN 20mg/dL and creatinine 0.7mg/dL. Intact PTH was 4pg/mL. ECG showed normal sinus rhythm and QT interval, but diffuse ST elevation. She was admitted for failure to thrive and hypercalcemia. Interventions included hydration and furosemide.
On hospital day (HD)2, IV steroids were added. Results from admission showed 25(OH)D 150ng/ml, (normal 30-100ng/ml) and 1,25(OH)D of 71ng/ml, (normal 24-86ng/ml). Renal ultrasound showed bilateral medullary nephrocalcinosis.
All other causes of hypercalcemia were ruled out. It was found that the patient's VD supplementation was 1ml of micellized VD 1000IU per 0.05mL drop, or 20,000IU daily since birth. On HD3 she was started on pamidronate, for 2 total doses.
Five weeks after discharge, 25-OHD level normalized, and her weight rose to the 90th percentile.
Conclusion: Pediatrician - parent communication is important in preventing VDI. Expansion of OTC formulations increases risk for misdosage. Accurate medication report should be obtained at each medical checkup. Initial symptoms of VD toxicity are nonspecific, thus important to consider VDI in the differential diagnosis of hypercalcemia.

P2-d1-721 Bone, Growth Plate and Mineral Metabolism 6

Vitamin D levels in children diagnosed with acute otitis media

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Objective and hypotheses: Viral and bacterial agents are both involved in the etiopathogenesis of acute otitis media (AOM). The purpose of this study was to investigate the relationship between Vitamin D deficiency and AOM infection.
Methods: The study group consisted of 88 ambulatory children diagnosed with AOM and 81 healthy children. Children aged between 1 and 13, who were free of any craniofacial abnormality, chronic diseases and acquired or congenital immunodeficiency were prospectively included. Healthy children with similar demographic characteristics were enrolled as the control group. Patients were divided into groups according to their serum 25(OH) Vitamin D levels.
Results: Serum 25(OH) Vitamin D levels in the study and control groups were 20.6 ± 10.2 ng/mL and 23.8 ± 10.3 ng/mL, respectively ($p< 0.05$). There was no statistically significant difference between the study and control groups in terms of parathormone and calcium levels ($p>0.05$).
Conclusions: 25(OH) Vitamin D levels being significantly lower in children diagnosed with AOM compared to the control group in the two otherwise similar groups suggests that Vitamin D deficiency plays a role in otitis media infection.

P2-d1-722 Bone, Growth Plate and Mineral Metabolism 6

Assessment of the effects of levothyroxine (LT-4) treatment on bone turnover parameters in children with subclinical hypothyroidism

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Objective and hypotheses: The aim of this study is to assess the effect of 6-month-long physiologic dose of L-T4 treatment on the metabolic bone markers in children with subclinical hypothyroidism.
Methods: In a group of 28 prepubertal children (10 girls) with a mean chronological age (CA) of 6.19 years, auxologic (height, weight, bone age (BA)) and biochemical data (serum sT_3, sT_4, TSH, Cr, Ca, P, BALP, Mg, PTH, 25-OH vitamin D_3, OC, PINP and urine Cr, Ca, P, NTx, DPyr) and bone mineral density were evaluated at the beginning and compared with those obtained after L-T4 treatment.
Results: CA-BA difference was significantly reduced in male cases after L-T4 treatment. TSH and sT_3 levels were reduced whereas sT_4 levels were increased significantly; all were within normal limits. Serum P and Mg levels and urine P excretion were reduced significantly. PINP levels were increased significantly while NTx/Cr levels were found to be significantly reduced. No differences in lomber and femoral BMD Z-scores.
Conclusions: After L-T4 treatment, the fact that BA/CA ratio stayed < 1 demonstrated that physiologic L-T4 treatment does not create any negative effect on BA. However, there was an improving effect on the somatic development as seen in male children. A decrease in sT_3 levels is the sign of euthyroid metabolism. A decrease in serum Mg levels pointed to the improvement in Mg retention after euthyroid metabolism. Changes in serum and urine phosphorus levels suggested that phosphorus might be used in bone formation and thyroid hormones have a direct effect on the phosphorus balance. An increase in PINP levels reflects stimulated osteoblastic activity while a decrease in NTx/Cr ratio indicates decreased osteoclastic activity. No change in BMD Z-score values proves that the physiologic dose of L-T4 treatment does not have any negative impact on bone mineral density.

P2-d1-723 Bone, Growth Plate and Mineral Metabolism 6

Calcium disorders in childhood malignancies in the University of Port Harcourt Teaching Hospital, Nigeria: when should bone mineral density studies start?

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Background: Children with cancers are fraught with several metabolic complications, which may be due to the disease processes or the treatment of the diseases. Calcium disorders are of major concern because they impact on the bone health of the children acutely or in the future. In our resource-limited setting, it is difficult and expensive to assess bone mineral density in the conventional ways, so it is necessary to find ways of extrapolating these deficiencies.
Objective and hypotheses: Analyse calcium levels in children with cancers.
Methods: A cross sectional data analysis of all children admitted in the oncology unit of the Paediatrics Department University of Port Harcourt Teaching Hospital was carried out between Jan, 2008 and Dec, 2012. Patients that had at least one serum calcium level evaluated were included in our study. Demography, serum calcium, phosphate, alkaline phosphatase and uric acid levels were retrieved from the case files. Also retrieved were the duration of disease before presentation, diagnosis, mode of therapy and disease outcome. Data was analysed using IBM SPSS version 20. Significant values were evaluated using chi square test and t values, and p value was significant if less than 0.05.
Results: Of the 78 children managed for cancers during the study period, only 66 had serum calcium levels measured for various reasons especially tumor lysis syndrome. There were 48 (72.7%) children who had low calcium levels and no child had hypercalcemia. Thirteen 13(92.9%) of the children with Burkitt's lymphoma and 14 (60.9%) of Wilm's tumor had hypocalcaemia. The longer the disease duration before presentation, the higher the number of children with hypocalcemia.
Conclusions: Serum calcium levels should be evaluated immediately a child is diagnosed with cancer. Compensatory mechanism may not be sufficient and the bone mineral density may be compromised, supplementation should start early.

P2-d1-724 Bone, Growth Plate and Mineral Metabolism 6

Hypocalcaemia and seizures in a 5-week-old girl due to autosomal dominant hypocalcaemia: a case study and review of the literature

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Background: Autosomal dominant hypocalcaemia (ADH) is caused by activating mutations in the calcium-sensing receptor (CaSR), which results in an inappropriate PTH response at low serum calcium levels. The clinical presentation varies from mild neurological symptoms to recurrent seizures, but some patients remain asymptomatic. The pediatric phenotype, however, is poorly defined.
Objective and hypotheses: We present a case of a severe ADH along with a thorough review of reported cases in children to provide an overview of the pediatric phenotype and prognosis.
Methods: We used DNA sequence analysis and bioinformatics, and systematically searched PubMed for pediatric cases of ADH.
Results: A five week old girl with no family history of hypocalcaemia and epilepsy presented with recurrent seizures lasting 1-5 minutes. Blood tests revealed low serum calcium-ion at 0.79 mmol/l, low PTH at 0.7 pmol/l and high phosphate at 3.24 mmol/l. ADH was suspected and molecular genetic analysis identified an undescribed activating mutation in the CaSR gene, a c.392G>C variant resulting in a cysteine to serine amino acid substitution at codon 131. We then identified 47 pediatric cases of ADH that were categorized into three groups based on their neurological symptoms. Seizures were most frequent in the youngest children, but were also seen among older children. Patients with severe neurological symptoms had significantly lower levels of calcium compared to asymptomatic and mildly affected patients ($P < 0.001$). The majority of patients were later diagnosed with nefrocalcinosis, nephrolithiasis and/or basal ganglia calcifications.
Conclusions: This study presents a new activating mutation in the CaSR resulting in severe hypocalcaemia and seizures. Review of pediatric ADH patients indicates that the younger children have the most severe presenting symptoms, but seizures were seen in a wide pediatric age range. ADH is an important diagnosis to consider in children with hypocalcaemia and low PTH.

P2-d1-725 Bone, Growth Plate and Mineral Metabolism 6

Improvement of growth and bone mineral density in two cases of osteogenesis imperfecta with recombinant human growth hormone therapy and pamidronate

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Objective: To inspects the effect and the adverse event of recombinant human GH (r-GH) in combination with bisphosphonate in pediatric osteogenesis imperfect (OI). We focused on possible improvement of bone mineral density (BMI) with DEXA, bone metabolism marker, growth velocity, and fractures risk.
Case 1: 8yr female with Type 2 OI. She was bone at 36 wks of gestation with weight of 1684g (-3.0 SDS), and length of 42cm (-2.1 SDS). She started pamidronate from 4.5 yr. She was height 85.5cm (-7.67 SDS), weight 13.9kg. Because she satisfied the criteria of GH therapy for SGA short stature, she was treated with 0.23 mg/kg/wk r-GH from 8.9 yr. BMD increased to 0.464gms/cm^2 from 0.626gms/cm^2 for three years. Growth velocity of before r-GH, first year, second year, and third year was 4.4 cm/yr, 6.2 cm/yr, 4.1 cm/yr, and 5.6 cm/yr, respectively. Height SDS improved 0.02 after three years. Bone fracture was one time for three years.
Case 2: 5 yr female with Type 3 OI. She was bone at 39 wks of gestation with weight of 2574g (-1.3 SDS), and length of 44cm (-2.8 SDS). She started pamidronate from 1 mo. She was height 85.5cm (-4.93 SDS), weight 13.9kg. Because she satisfied the criteria of GH therapy for SGA short stature, she was treated with 0.23mg/kg/wk r-GH from 5.1 years-old. BMD increased to 0.701gms/cm^2 from 0.468gms/cm^2 for three years. Growth velocity of before r-GH, first year, second year, and third year was 3.1 cm/yr, 9.8 cm/yr, 6.1 cm/yr, and 5.2 cm/yr, respectively. Height SDS improved 1.5 for three years. Bone fracture was one time for three years.
Conclusions: The combined r-GH and pamidronate treatment improved growth velocity and BMD without the increase of a fracture risk.

P2-d1-726 Bone, Growth Plate and Mineral Metabolism 6

Association of serum 25-hydroxyvitamin D concentration and metabolic syndrome in Korean children and adolescents

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Background: Vitamin D is required not only for bone health but also has been reported to play a role in a range of ailments such as autoimmune disease, cardiovascular disease, type 2 diabetes, hypertension, depression, and certain types of cancer. Several studies have reported that poor vitamin D status during childhood and adolescence is related to obesity and metabolic syndrome.
Objective and hypotheses: We investigated the association between serum 25(OH)D concentrations and the presence of metabolic syndrome components in Korean children and adolescents.
Methods: 141 Korean children and adolescents aged 6 to 18 were enrolled. Anthropometric data including height, weight, body mass index (BMI, kg/m^2), waist circumference, and blood pressure were obtained. 25(OH)D, serum lipid, fasting plasma glucose (FPG), and insulin were measured and HOMA-IR was calculated. Metabolic syndrome in this study was defined by modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).

Results: Among total 141 subjects, 26 (18.4%) children and adolescents had metabolic syndrome. Children and adolescents who have metabolic syndrome have significantly lower serum 25(OH)D concentration than those who do not have (12.35 ± 4.65 vs. 14.81 ± 4.63 ng/mL) (p=0.015). Waist circumference, SBP, fasting plasma glucose, insulin, HOMA-IR are significantly correlated with serum 25(OH)D concentration (p< 0.05). Only LDL-cholesterol is significantly different according to tertile groups of serum 25(OH)D concentration. The odds ratio of group I (25(OH)D < 11.50 ng/mL) is 1.826 compared to group III (25(OH)D >16.30 ng/mL).
Conclusions: Children and adolescents who have metabolic syndrome have lower serum 25(OH)D concentration. The prevalence of metabolic syndrome may be higher in children and adolescents with severe 25(OH)D deficiency.

P2-d1-727 Bone, Growth Plate and Mineral Metabolism 6

Effects of steroid treatment on bone mineral density in children with nephrotic syndrome and congenital adrenal hyperplasia: comparison between drug or replacement therapy

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Background: Glucocorticoid treatment (GCt) is the most frequent cause of drug-induced bone loss. Glucocorticoid-sensitive nephrotic syndrome (GSNS) and congenital adrenal hyperplasia (CAH) need of GCt. GSNS becomes quiescent during high dose of GCs, and CAH needs of chronic GCt to replace cortisol deficit.
Objective: To compare the effects of high dose of GCs versus long-term GC replacement treatment on bone mineral density (BMD) by using peripheral quantitative computed tomography (QUS).
Pupulation and methods: We enrolled 40 participants: 20 CAH (10 F, mean age 13.4 +/- 6.9) on hydrocortisone treatment (mean duration 9.6 +/- 6 yrs; dose ranging from 7.26 to 25 mg/m^2 die); 20 GSNS (9 F, mean age 12 +/- 3.6) on prednisone treatment (mean duration 5.21 +/- 3.0 yrs; dose ranging from 60 mg/m^2 die at the onset to 4.5 mg/m^2 die during maintenance). Patients underwent QUS measurements at proximal phalanges of the non-dominant hand to assess bone quality, measured as amplitude-dependent speed of sound (Ad-SoS) and bone transmission time (BTT). Biomarkers of bone turnover and vitamin D status were also assessed.
Results: Significant differences were found for Ad-SoS and BTT between CAH and GSNS patients (p< 0.001): 14 GSNS patients (70%) had ultrasonometry parameters (UP) at lower limit of normal range (z score < -1), 3 (15%) had low bone mineral status (z score < -2), 3 (15%) were normal (z score >-1). UP were normal in CAH subjects. In GSNS patients, the low BMD did not correlate with treatment duration. Interestingly, GSNS patients had higher 25-hydroxyvitamin D levels than CAH subjects (33 +/- 4.6 vs 19 +/- 2.1 nmol/L; p< 0.01).
Conclusion: This study documented different effects on BMD in GSNS subjects on high-dose of GCs compared to CAH patients on replacement GCt. BMD in GSNS did not correlate with treatment duration but with cumulative dose of prednisone.

P2-d1-728 Bone, Growth Plate and Mineral Metabolism 6

Short-term intravenous calcium infusion followed by high dose oral calcium therapy in hereditary vitamin D resistant rickets

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Introduction: Hereditary 1α,25 dihdroxy vitamin D resistant rickets (HVDRR) is a rare autosomal recessive disorder. Children with HVDRR present with severe form of rickets in early infancy and variable degree of alopecia. Biochemistry profile in HVDRR shows low calcium and phosphate with elevated alkaline phosphatase, parathyroid hormone and1α,25 dihdroxy vitamin D. High dose calcium therapy has shown clinical improvement and resolution of clinical and radiological rickets. This indicates that optimal calcium level can achieve normal bone mineralization independent of vitamin D receptor activity.
Case study: We are reporting three male siblings age 12, 7 and 1.5 years born to consanguineous parents with severe rickets and alopecia. Diagnosis of VDRR is based on clinical and biochemical profile including low calcium and phosphate with elevated alkaline phosphate, parathyroid hormone and 1α,25 dihdroxy vitamin D. First two siblings were treated with 3-7 days IV calcium infusion every month and oral calcium therapy since the age of 2 years. This treatment did not resolve rickets and biochemical profile. We treated older two siblings with 1.5g/m^2 and younger child with 750 mg/ m^2 daily calcium infusion for 4 weeks. They were discharge on oral high dose calcium therapy. Biochemical profile improvement is shown in table 1.

	Calcium before Infusion mmol/L	Calcium after Infusion mmol/L	After one month of oral calcium	Oral Calcium dose	AlP IU/L a) before infusion b)after infusion	PTH ng/L a) before infusion b)after infusion
Sibling1	1.69	2.17	2.10	7.2g/m2	a)392 b)314	a)502 b)139.6
Sibling 2	1.72	2.24	2.01	9g/m2	a)1014 b)842	a)409.9 b)208
Siblin 3	1.89	2.22	2.10	6g/m2	a)1407 b)998	a)796.4 b)325.6

[Table1]

Clinically older siblings reported complete resolution of bone pain and increased mobility with minimal tiredness, these finding remained same after 1 month of oral calcium. Younger sibling 1.5 year old started weight bearing by the end of 4 weeks infusion.
Conclusion: Short term daily calcium infusion for 4-6 weeks with improvement of bone markers can reduce the calcium demand of hungry bones. It can be followed by high dose oral calcium to heal the rickets.

P2-d1-729 Bone, Growth Plate and Mineral Metabolism 6

Ceasing vitamin D replacement in infants with premature closure of frontal fontanelle: true or false?

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Background: As the deficiency of vitamin D is known to delay the closure of anterior fontanel, infants with premature closure of anterior fontanel are thought to have vitamin D excess and cessation of vitamin D prophylaxis is the first thing that comes to mind.
Objective and hypotheses: The aim of this prospective controlled study was to evaluate the effect of vitamin D levels and the amount of vitamin D prophylaxis on fontanel closure in neonatal and infantil periods.
Methods: A total of 50 outpatients that were admitted to pediatric endocrinology department with premature anterior fontanel closure were included. A total of 35 healthy infants with the same age and gender who had open anterior fontanels were considered as the control group.
Results: Serum vitamin D levels were found to be lower, whereas parathormone (PTH) levels were significantly higher in patients with premature closure of anterior fontanel. When the patients who had been ceased of vitamin D support were compared with the regular vitamin D takers, a significant

difference was observed in terms of alkaline phosphatase (ALP) and PTH levels. Even though there was no significant difference with respect to serum vitamin D and calcium levels, the levels were lower in the patients who had been ceased of vitamin D support.
Conclusions: Many infants with early anterior fontanel close were determined to have even normal and/or lower vitamin D levels. Therefore, it may be suggested for pediatricians and practitioners to continue vitamin D prophylaxis in infants who had premature closure of anterior fontanel.

P2-d1-730 Bone, Growth Plate and Mineral Metabolism 6

Vitamin D levels in adolescent inpatients with eating disorders

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Background: Anorexia nervosa (AN) is a common cause of low bone mass among adolescents and young women. Previous studies assessing the vitamin D status of teenagers with AN, with its implications for bone health, showed inconsistent results.
Objective and hypotheses: To assess vitamin D status in a large cohort of adolescent inpatients with eating disorders. We hypothesized that vitamin D levels of AN patients will be lower compared with patients with other eating disorders and will further decrease during hospitalization.
Methods: 25-hydroxyvitamin D (25OHD), calcium, and phosphorus levels as well as bone density were measured in 87 adolescent inpatients (aged 15.9±2y, Female=78) with eating disorders (AN=64;Bulemia nervosa=5; Eating disorders NOS=18).
Results: Mean 25OHD levels were 24.1±7.5ng/ml. Vitamin D deficiency (< 15ng/ml) was found in 7.8% of the patients, and insufficiency (15-20ng/ml) in 22.2%. Only16.7% of patients had levels>32ng/ml, believed by many experts to be optimal. No association was found with age, gender, bone density, height-SDS, BMI-SDS, disease type, a diagnosis of depression, or calcium, phosphorus or alkaline phosphatase levels. 25OHD levels during winter were significantly (< 0.001) lower than summer levels. Disease type or depression were not associated with lower 25OHD levels. 25OHD levels did not change during hospitalization.
Conclusions: Adolescents with AN had 25OHD levels similar to levels previously described in Israeli adolescents. Unlike previous studies, we did not find an association between 25OHD levels and age, gender, weight status or presence of depression. The significant effect of season suggests that 25OHD levels did not reflect vitamin supplementation. Given the risk for osteopenia and osteoporosis in this population, 25OHD levels found in this patient group may not offer optimal bone protection.

P2-d1-731 Bone, Growth Plate and Mineral Metabolism 6

Clinical course and etiology of primary hypoparathyroidism in childhood

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Background: Hypoparathyroidism is a rare disorder with varying clinical manifestation from asymptomatic hypocalcemia to hypocalcemic seizure.
Objective and hypotheses: This study was undertaken to characterize etiology and clinical course of hypoparathyroidism in childhood.
Methods: The study included 30 pediatric patients (20 males and 10 females) with primary hypoparathyroidism diagnosed in single institution. Clinical features, endocrine data, molecular studies and radiologic finding were reviewed retrospectively.
Results: Etiologies of hypoparathyroidism were DiGeorge syndrome (66.6%), Barakat or HDR (Hypoparathyroidism, deafness, and renal dysplasia) syndrome (10%), autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) (3.3%), Kearns-Sayre syndrome (3.3%), and idiopathic (16.7%). Their median age at diagnosis was 2.5 years (range; 1 day-16 years). They have been followed-up for 6.7 yrs (range; 1month-22yrs). Patients with DiGeorge syndrome were diagnosed earlier than those with other causes of hypoparathryoidism (103 days vs 7.0 years, p= 0.008).
Among 20 patients with DiGeorge syndrome, 13 patients (65%) showed transient hypoparathyroidism. Average dose of calcium supplementation was 32.29±21.8 mg/kg/day and 66.7% of patients were prescribed calcitriol (0.031±0.025 mcg/kg/day). Medullary nephrocalcinosis was demonstrated in about quarter of patients on renal ultrasound. Asymptomatic basal ganglia calcification was observed in about half of patients. Renal complications included nephrocalcinosis, and chronic renal insufficiency.
Conclusions: DiGeorge syndrome is the most common cause of primary hypoparathyroidism. Monitoring for renal complication should be considered in patients with hypoparathyroidism during calcium supplementation.

P2-d1-732 Endocrine Oncology 1

Chemosensitization of leukaemia cells through an inhibition of Nampt

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Background: Nampt (Nicotinamide phosphoribosyltransferase) catalyzes the rate-limiting step in the NAD-biosynthetic pathway from nicotinamide, regulates intracellular NAD concentrations and the activity of NAD-dependent enzymes. Cancer cells are highly dependent on NAD for energy and DNA repair processes and are expected to be more susceptible to the inhibition of NAD synthesis than non-transformed cells.
Hypothesis: Inhibition of Nampt by FK866 sensitises leukemia cells for chemotherapeutic agents (CAs).
Methods: Jurkat and MOLT-4 cell lines were used as leukemia cell models. Viability was measured using WST-1 assay. Cell death was analysed by propidium iodide staining. Western Blotting was performed to detect Nampt protein levels. NAD levels were measured using HPLC and a colorimetric NAD/NADH assay. Enzymatic activity of Nampt was measured in lysates of leukemia cells and peripheral blood mononuclear cells (PBMCs) using ^{14}C-nicotinamide.
Results: Nampt expression and enzymatic activity was significantly higher in leukemia cell lines compared to normal PBMCs. The combination of CAs (etoposide, doxorubicin and methotrexate) and FK866 decreased cell viability to a greater extend than each substance alone. The combination of etoposide and FK866 also caused an increased cytotoxic effect. Nampt activity was reduced by incubation with 10nM FK866 (91.0±12.7%) for 24 h. CAs had no further decreasing effect on Nampt activity. Intracellular NAD levels were decreased after stimulation with 10nM FK866 alone (77.5±4.5%). The combination with CAs had no additional effect. Nampt protein levels of leukemia cells incubated with FK866 and CAs were not changed in lysates.
However, Nampt protein levels were increased in the supernatant after etoposide stimulation or in combination with FK866.
Conclusion: A combination of FK866 and CAs could be a novel therapeutical strategy to enhance the effectivity of CAs in lower doses resulting in less adverse side effects of chemotherapy.

P2-d1-733 Endocrine Oncology 1

A girl with androgen secreting adrenal oncocytoma

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Introduction: Adrenal oncocytoma is an extremely rare neoplasm, most often nonfunctioning, with less than 150 cases reported to date. To our knowledge only 3 cases of functioning adrenal oncocytoma in children were described.
Clinical case study: We report a case of androgen producing adrenal oncocytoma in a 9-year-old girl. She presented to our clinic with severe virilization, first signs of which were noticed 7 months before proper diagnosis. During hormonal investigations we found elevated androgens: testosterone 17.8 nmol/l (referent range 0.5-2.6), 17-OH-Progesteron 2.21 nmol/l (0.4-1.55), DHEA-S 13.9 nmol/l (0.95-11.67), androstendione 3.7 ng/l (0.4-3.4).
Imaging studies revealed mass in the area of the left adrenal gland. The tumor was well defined, low in lipids, approximately 23 mm in diameter. Laparoscopic left adrenalectomy was performed and the tumor was removed along with the adrenal gland. Histological findings were consistent with benign adrenal oncocytoma. During the postoperative period hormonal levels returned to normal. No cortisol deficiency was found. For the first two weeks after the rapid drop of testosterone levels the girl suffered severe mood swings, irritability and lethargy.
On follow-up, one month after removal of the tumor, we found pubertal levels of gonadotropins and isosexual sex hormones. So far there are no signs of recurrence . In 6 months after the surgical removal of the tumor, decreasing of virilization is visible.
Conclusion: Since adrenal oncocytoma is extremely rare, there are no established quidelines for specific management. Questions about hormonal and recurrence follow-up also remain to be answered.

P2-d1-734 Endocrine Oncology 1

Risk of metabolic syndrome in adolescents treated for liquid and solid non-central tumors

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Background: The improving survival rate in childhood cancer allowed us to better understand treatment-related late effects. An important health concern in these patients is metabolic syndrome (MS).
Objective: Primary objective of the study was to assess the prevalence of MS in adolescents (10-16 years) with 2 years off-therapy after a diagnosis for childhood malignancy. Secondary objective was to identify risk factors for MS.
Methods: One hundred patients treated for liquid and solid non-central tumors underwent BMI-SDS, waist circumference (WC), blood pressure evaluations and biochemical measures for high-sensitive PCR, lipids and glucose metabolism. Homeostasis Model Assessment (HOMA) index was calculated. MS was defined based on the International Diabetes Federation criteria. Patients were categorised in: normal (BMI < 90°centile and none risk factors), moderate risk (BMI>90°centile and none risk factors or BMI < 90°centile and ≥ 1 risk factors), high risk (BMI>90°centile and 1 risk factors), MS (BMI>90°centile and ≥2 risk factors).
Results: We found a 15% prevalence of MS (80%male, P=0.07), of whom 33.3% with neuroblastoma, 33.3% with bones tumors, 20% with LLA. In 93.3% of these subjects a WC > 90° centile was present. No significant correlations were found with hematopoietic cell transplantation, specific treatment protocols or secondary endocrinopathies. A WC >90° centile was present in 55% of the cohort overall, a high risk for MS in 40% and obesity in 62%. Levels of insulin, HOMA and LDL tended to be increased after total body irradiation, abdominal and thoracic radiotherapies and alkylating-anthracycline therapies (P's not significant).
Conclusions: Preliminary data support the concept that more than half of adolescents long term survivors for childhood cancer might be at risk for MS and that male gender and solid non central tumors might be additional risk factors independently of treatment protocols or secondary endocrinopathies.

P2-d1-735 Endocrine Oncology 1

Spectacular shrinkage of a giant, invasive and resistant paediatric prolactinoma under temozolomide

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Prolactinomas are rare in children and adolescents. Resistant forms are relatively rare. Our aim is to report a spectacular shrinkage of a giant prolactinoma, resistant to medical treatment that responded to Temozolomide.
Observation: A young woman aged 27, consulted for the first time at 17 years old for primary amenorrhea caused by an invasive prolactinoma (PRL=1350ng/ml, tumour size=23x30x17mm). She was treated by bromocriptine, cabergoline, then both for 8 years. The process remained stable, but PRL was never normalized. Then after, PRL increased and the tumour became giant and multidirectional. After an unsuccessful treatment by somatostatin analogues, she was operated on twice without any modification. Immuno-histochemy was positive for Prolactin, ki=5%, P53 negative. Post operative PRL = 19984ng/ml, and tumour size=55x63x48mm. As radiotherapy was refused, she continued medical treatment. Then, visual acuity decreased dramatically after several apoplectic episodes, but without any modification of the tumour volume, which pushed us to use Tomozolomide which reduces PRL and tumour height (respectively 11085ng/ml, and 29 mm=49% reduction) with a spectacular increase in visual acuity.
Conclusion: Although rare resistant prolactinomas are difficult to manage especially in young people. But, Temozolomide a cytostatic agent is apparently a good alternative for refractory tumours.

P2-d1-736 Endocrine Oncology 1

Follow-up of endocrine functions in children treated for malignant haemopathies: careful attention must be payed to the body weight even in cases of chemotherapy only

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Background: Malignant haemopathies are the most common cancers in childhood. Improvements in therapy have resulted in increased survival with long term complications. Endocrine disorders are among the most frequent of them specially because of direct damage to the hypothalamic-pituitary axis.
Objective and hypotheses: Of the present study was to analyze the endocrine monitoring of subjects treated at Rouen University Hospital before 18 years of age for acute lymphoblastic leukemia (ALL) or myeloid (AML) or non-Hodgkin lymphoma (NHL) between 1995 and 2000.
M**ethods:** Age at diagnosis, type (chemotherapy, radiotherapy and / or transplantation) and duration of treatment as well as clinical (height, weight, pubertal stage) and biological parameters (thyroid, growth hormone and /or gonadotropin) during and after therapy were collected retrospectively.
Results: Among the 40 subjects (18 girls, 22 boys) investigated diagnosed at a mean age of 5.3 years [0-12] (24 ALL, 10 AML, 6 NHL), overweight (BMI> 97%) was the most frequent complication observed in 9 patients (22%; 4 girls, 5 boys) at a mean age of 14.8 years [10.8-16.5]) and 8 years [3.5-11] after the first therapy for hemopathy. 5 out of those children were treated by chimiotherapy only. Other endocrine dysfunction was found in 9 children affecting gonadotropic (n= 6 girls), thyreotropic (n=2 boys) and somatotropic (n=3 boys) axis. Note that boys are rarely monitored in term of gonadotropic function.
Conclusion: Overweight is the most common observed endocrine anomalies in children treated for malignant haemopathies whatever the therapy used,

underlining the need of special extend attention on diet and lifestyle for ongoing health consequences. In addition, further systematic studies implicating pediatric hematologist and endocrinologists need to be performed to conclude about the prevalence and the prognostics factors of endocrine dysfunction.

P2-d1-737 Endocrine Oncology 1

Multicenter study on final height and body mass index in adult survivors of childhood acute lymphoblastic leukaemia treated on AIEOP 87-2000 protocols excluding cranial radiotherapy

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Background: In acute lymphoblastic leukemia (ALL), cranial radiotherapy (CRT) and methotrexate are an essential component in preventing meningeal relapse. No long-term auxological data on ALL survivors treated without CRT have been described yet.
Objective: To investigate the effect of chemotherapy alone (CT) on BMI and FH in a cohort of childhood ALL survivors.
Methods: Of 162 caucasian patients treated on AIEOP 87- 2000 protocols without CRT, 107 met inclusion criteria. Height- and BMI-SDS were collected at: diagnosis (dT); end of CT (eT); FH.
Results: Height-SDS decreased over the course of CT and up to FH both in males (M) and females (F). At diagnosis F had a significantly lower BMI-SDS than M, but it increased significantly during follow-up, until FH. The increase of male BMI-SDS during CT was greater than in F, but it decreased later.

	dT	eT	FH
Height SDS			
Total Population	0.61 ± 1.04	0.25 ± 1.08*	0.18 ± 1.13*
Male	0.62 ± 1.05	0.30 ± 1.09*	0.27 ± 1.03*
Female	0.60 ± 1.05	0.19 ± 1.09*	0.07 ± 1.25*
BMI SDS			
Total Population	0.15 ± 1.32	0.58 ± 1.34 *	0.51 ± 1.03*
Male	0.39 ± 1.30	0.82 ± 1.29*	0.49 ± 1.09°
Female	-0.12 ± 1.31†	0.29 ± 1.36*†	0.54 ± 0.96*

*[stat significance *vs. dT, ° vs. eT, † M vs. F]*

In total population, final BMI SDS significantly correlated with height- and BMI-SDS at dT (r 0.40, p 0.003; r 0.35, p 0.009, respectively) and with the variation of BMI SDS after CT (r 0.34, p 0.013). In addition, multivariate regression analysis identified F gender, height- and BMI-SDS at dT as independent predictive factors for final BMI-SDS.
Conclusions: In our study, survivors of childhood ALL treated with CT experienced reduction in height-SDS during CT that persisted until FH. Nevertheless, they generally seemed to achieve a normal FH with a BMI within the normal range. Even if all patients experienced an increase of BMI-SDS during CT, only F seemed at risk to conserve it until FH.

P2-d1-738 Endocrine Oncology 1

Water and electrolyte disorders in a large cohort of 159 paediatric patients with suprasellar tumours - at a distance from surgery

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Background: Patients with brain tumours have great risk of water and electrolyte disorders. Syndrome of inadequate ADH secretion (SIADH) and salt-wasting syndrome (SWS) are usually transient and linked to surgery or haemorrhage. Diabetes insipidus (DI) after surgery may be transient or permanent. Few studies focus on long term incidence of these disorders.
Objective: To describe incidence of long term water and electrolytes disorders in patients with suprasellar tumours, and association with other hormonal deficiencies.
Methods: Retrospective study. Patients with suprasellar tumours seen in consultation between 2007-2011 at Hôpital Necker, Institut Gustave Roussy or Institut Curie were included. Disorder was noted if present >1 month after surgery. Patients receiving no treatment or who died before treatment completion were excluded.
Results: 159 patients with suprasellar tumours were included, 54,1% were girls. Tumour type: glioma (43,4%), craniopharyngioma (43,4%), germinoma (11,3%), others (1,9%). Age at diagnosis: 7,1±4,6 years. DI was present at diagnosis in 16,2%. SIADH was present at diagnosis in 1 patient and disappeared during treatment. DI was the most common disorder observed after treatment (50,3%), and was associated with treatment ($p< 0,001$), mainly surgery. SWS was present in 3,6% and SIADH was rare (1,2%).
1 hypernatremia was due to adipsia, 3 patients with hyponatremia were unclassifiable (insufficient data).
2 postsurgical DI showed spontaneous recovery after more than 1 year. TSH deficiency after treatment was noted in 68,9% of patients tested, ACTH deficiency, in 66,2%. Thirst was scarcely documented, reported excessive in 5 patients and absent in 5.
Conclusions: Patients with suprasellar tumours have a high incidence of long term water and electrolyte disorders, DI being the most common. SWS may be persistent and need supplementation during several months. Assessment of thyrotroph and corticotroph function is important, as well as thirst sensation.

P2-d1-739 Endocrine Oncology 1

An audit of endocrine late effects in survivors of childhood brain tumours

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Background: Brain tumours are the most common solid tumour in children, affecting 400 children in the UK each year. The aggressive treatment required for cure, may have serious consequences, of which endocrine late effects are the most prevalent.
Objective and hypotheses: The aim of this audit was to ascertain the frequency and nature of endocrine late effects; in a cohort of 30 survivors of childhood brain tumours, diagnosed over a fourteen year period.

Methods: Data was collected on tumour site, histology, treatments used & endocrine complications.
Results: Mean age at diagnosis was 5.8yrs. Commonest tumour location was posterior fossa; commonest tumour type was glioma. 70% of children underwent surgery, 87% received chemotherapy, 40% received cranial radiotherapy, 23% received craniospinal radiotherapy & 16% children received both cranial & craniospinal radiotherapy.
57% of survivors were referred to the Endocrine clinic, at a mean duration of 1 year following end of treatment.
37% of survivors were diagnosed with growth hormone deficiency (all of these children had received radiotherapy). Impaired spinal growth was seen in all children who received craniospinal radiotherapy.
23% of children were found to have a suboptimal cortisol response; necessitating emergency hydrocortisone treatment.
20% of survivors developed hypothyroidism; all of these children had received radiotherapy. Onset ranged from 1 to 5 years following treatment.
10% of survivors were diagnosed with precocious puberty; which in 1 case had masked a growth hormone deficiency.
34% of children had multiple hormone deficiencies.
Conclusions: This audit shows the high prevalence of endocrine late effects in survivors of childhood brain tumours. Growth hormone deficiency was the most common, however high prevalence of multiple hormone deficiencies. Data support the establishment of a joint oncology & endocrinology late effects clinic; to ensure early identification & treatment of these serious complications.

P2-d1-740 Endocrine Oncology 1

Tumor origin and growth pattern at diagnosis and surgical hypothalamic damage predict obesity in paediatric craniopharyngioma

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Background: Severe obesity is a major problem in pediatric craniopharyngioma.
Objective and hypotheses: We investigated whether tumor origin, growth pattern, and surgical damage predict obesity in pediatric craniopharyngioma.
Methods: Subjects were 58 patients (30 males) with no tumor recurrence during the first postoperative 18 months. Preoperative hypothalamic involvement was classified into no (pre_G0, n = 19), low (pre_G1, n = 21), and severe (pre_G2, n = 18) involvement groups based on sub- or supradiaphragmatic tumor origin and growth patterns. Postoperative hypothalamic involvement was classified into no (post_G0, n = 4), minimal (post_G1, n = 19), and significant (post_G2, n = 35) involvement groups according to follow-up imaging.
Results: The prevalence of obesity increased from 13.2% at diagnosis (mean age = 8.1 years) to 37.9% at last follow-up (mean duration = 9.1 years). Only the body mass index (BMI) Z-score increment of the first postoperative year (first-year DBMI_Z) was significant (P = 0.007). Both the preoperative BMI_Z (P = 0.001) and the first-year DBMI_Z (P = 0.017) showed an increasing trend from the pre_G0 to pre_G1 to pre_G2 group. For the 40 patients with pre_G0 or pre_G1, the first-year DBMI_Z was higher in the post_G2 group than the post_G1 group (0.02 ± 0.91 vs. 0.89 ± 0.72, P = 0.003).
Conclusions: Tumor origin and growth pattern affect preoperative BMI_Z and postoperative weight gain. Despite no or low hypothalamic involvement at diagnosis, surgical damage contributes to postoperative weight gain in patients with craniopharyngioma.

P2-d1-741 Fat Metabolism, Obesity 7

Effect of weight loss on markers of inflammation and endothelial function in obese children and adolescents

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Background: Obesity is associated with low-grade inflammation and hyperinsulinism that may influence the progression of endothelial dysfunction already in childhood.
Objective: To detect variations in metabolic profile and markers of inflammation and endothelial activation [interleukin-6 (IL-6), endogenous secretory receptor of advanced glycation end products (esRAGE) and endothelin (ET-1)] in children with primary severe obesity before and after weight loss.
Methods: Prospective study involving 14 obese children (Ob) (11.0 ± 0.1 yr) that underwent an 1-year-long lifestyle intervention and 18 normal weighted subjects (C) (10.4 ± 3.6 yr). In Ob, anthropometric data were assessed both at baseline (time 0) and after intervention (time 1) together with oral glucose tolerance test (OGTT) and IL-6, ET-1 and esRAGE levels.
Results: At time 0, serum IL-6 and ET-1 levels resulted significantly higher in Ob respect to C (12.9 ± 8.8 vs. 4.8 ± 1.19, p 0.00; 9.3 ± 4.5 vs. 6.1 ± 4.2, p 0.04; respectively). After weight loss, Ob significantly improved glucose metabolism and they showed a significant reduction of IL-6 and ET-1.

	Time 0	Time 1	p
BMI (SDS)	2.9 ± 0.4	2.2 ± 0.5	0.00
Glycemia after 120 min.OGTT(mg/dl)	103.6 ± 14.4	87.1 ± 14.5	0.00
Insulin after 120 min.OGTT(mIU/L)	84.5 ± 39.5	55.2 ± 24.5	0.02
IL-6 (pg/ml)	12.96 ± 8.8	5.6 ± 4.9	0.01
ET-1(pg/ml)	9.35 ± 4.5	5.46 ± 4.4	0.03
esRAGE (ng/ml)	0.37 ± 0.1	0.47 ± 0.17	0.1

[Obese patients]

Multivariate regression analysis identified the reduction of BMI after weight loss as significant predictive factor for reduction of ET-1.
Conclusions: Our results demonstrated higher concentrations of inflammatory markers in obese children compared to healthy subjects. Nevertheless, an early lifestyle intervention could improve the levels of these molecules together with glucose metabolism and may reverse the development of premature endothelial dysfunction in obese children.

P2-d1-742 Fat Metabolism, Obesity 7

The relationship between hepcidin concentrations in serum with iron homeostasis in obese children

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Background: Obesity is associated with elevated markers of inflammation such as high sensitive CRP and IL-6. Hepcidin, a key regulator of iron homeostasis, decreases the absorbtion of dietary iron and the release of recycled iron from macrophages. Recently Hepcidin expression in adipose tissue has been described. Furthermore, IL-6 activates hepcidin transcription and expression
Objective and hypotheses: We aimed to assess the association between poor iron status and obesity and to investigate whether iron homeostasis of obese children may be modulated by variations in serum hepcidin.
Methods: This case control study included 50 obese (BMI>95%) and 50 non-obese children aged 8-18 yrs. Parameters of iron status (hemoglobin, MCV, serum iron, ferritin, total iron binding capacity and transferrin saturation), serum hepcidin and IL-6 levels were assessed.

Results: Obese children showed significantly lower iron, hemoglobin, MCV, ferritin and transferrin saturation ($p < 0.05$) but higher hepcidin and IL-6 levels ($p = 0.024$, $p< 0.05$ respectively) compared with controls. A direct correlation between hepcidin and IL-6 levels ($P< 0.0001$), and inverse correlations between hepcidin and iron ($P = 0.024$), hepcidin and hemoglobin ($P = 0.001$), and hepcidin and MCV ($P = 0.02$) were observed.
Conclusions: The chronic inflammatory state in obesity leads to elevated hepcidin levels and results in the low iron status.

P2-d1-743 Fat Metabolism, Obesity 7

Improvement in anxiety-depression manifestations, eating behavior and growth velocity by exercise in obese children with moderate short stature

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Background: In obese children, anxiety and depression (A-D) are frequent and worsen eating habits. Obesity alters neuronal transmission and serotonin reuptake. Exercise improves behavioral, neurotransmission and release of molecules of well-being; stimulates secretion of GH which has diagnostic application in the Exercise Test (ET). We observed in sedentary obese children with stature in the low percentiles or under epigenetics size (SOBSL), the GH response to ET is poor. In other glands cell sensitization is done to improve secretory response.
Objective and hypotheses: Assess the psychological clinical changes produced by aerobic exercise 1 hour a day (AE1H) for six months, in children SOBSL with A-D and the changes in the GH response to ET as well as in growth velocity (GV).
Methods: 20 boys and 10 girls SOBSL, 8 to 9 years old, with size PC 5 to 25 for age, no nutritional deficiency, endocrine, parasitic or organic disorder, with slow and constant GV in the last year, prepubertal, BMI 31-38, with poor ET response to stimulation of GH and moderately high score (25 to 35) in the Hamilton Test (HT), so, moderate A-D, most with family environment deteriorated, entered a supervised program AE1H and normocaloric diet, for a period of six months, after which was reevaluated ET, GV, BMI and A-D
Results: They Improve HT (score 9-15) ($p < 0.001$ *t* Test) A-D, their social and family relationships, diet compliance and weight loss, BMI 22-30 ($p < 0.001$ *t* Test). The response of GH in ET (Δ) rose significantly ($p< 0.01$ *t* Test) at the end of the EA1H program in relation to beginning and accelerate GV ($p< 0,05$)
Conclusions: AE1H benefit SOBSL, improving A-D tendencies for which should be used more widely in these patients to prevent psychological worsening. The second benefit is a better GH response to the ET and the acceleration of GV suggesting that exercise sensitizes the somatotrophs to respond in greater magnitude to ET with the consequent therapeutic applicability of exercise.

P2-d1-744 Fat Metabolism, Obesity 7

Early puberty in obese girls: effect of weight reduction on menarche timing

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Background: Early onset of puberty is a common event in obese girls and usually produce early menarche, increasing parents anxiety and lead them to search for hormonal therapy to stop puberty progression and avoiding early menarche.
Objective and hypotheses: Evaluate the effect of weight reduction on puberty progression
Methods: We studied 220 obese girls who started breast development Tanner 2, between 8 and 9 years. Body mass index (BMI) was ≥ 95 Percentile. Bone age was 1.2 ± 0.5 years more than chronological age. Genetic and hormonal anomalies were excluded. Management with dietary therapy and exercise started and patients were evaluated every 3 months. Weight, height, BMI and, Tanner stage pubertal progression were recorded. Bone age was determined every year. Observation period was 3 years.
Results: 90 girls (40 %) (Group 1) achieved continues and maintained weight reduction through the 2 year observation period of the study and BMI were established between percentile 75-85. Weight reduction was 2.3 ± 0.5 kilograms. The other 130 girls (group 2) reduced weight the first evaluation and then started gaining weight after. Parents Lake of cooperation was the main cause of failure to maintain weight reduction. Menarche started at age of 11.5 ± 0.3 years in-group 1, while in-group 2, it started at age 10.7 ± 0.2 years, a difference of almost 10 months earlier than group 1.
Conclusions: Moderate weight reduction in obese girls, in addition to its benefit in health, is a safe and simple way to avoid early age of menarche in obese girls, and may help to avoid parents anxiety regarding pubertal development of their children.

P2-d1-745 Fat Metabolism, Obesity 7

Changes in metabolic syndrome and fibrinolysis as a function of BMI, insulin resistance and leptin levels following lifestyle intervention in obese prepubertal children

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Objective: To evaluate disorders associated with the metabolic syndrome in obese prepubertal children and assess improvements in status as a function of BMI, insulin resistance and leptin levels after nine months' treatment.
Methods: Cross-sectional and longitudinal studies were carried out in obese children.
Subjects: Fifty obese children (aged 6 - 9 y) and fifty non-obese children (control group), matched by age and sex.
Antropometric parameters, glucose, insulin, HOMA-IR, leptin, plasminogen activator inhibitor-1 (PAI-1), lipid profile and a number of parameters related to obesity and the metabolic syndrome were studied at baseline (in obese and control groups) and after nine months' treatment (in obese children).
Results: Cross-Sectional Study: The mean values for HOMA-IR, systolic blood pressure (SBP), diastolic blood pressure (DBP), uric acid, triglycerides, leptin and PA-1 were significantly higher in obese children than in controls. HDLc and Apo A-1 were significantly lower.
Longitudinal Study (obese group): After nine months, children with lowered SDS-BMI displayed a significant decrease in insulin, HOMA-IR, DBP, uric acid, PAI-1, leptin and triglyceride levels compared to obese children with stable SDS-BMI status, together with a significant increase in HDLc.
Only SDS-BMI was found to be an independent predictive factor for changes in leptin concentration, whilst HOMA-IR and leptin were independent predictive factors for changes in triglyceride levels. Only leptin proved to be an independent predictive factor for PAI-1.
Conclusions: Obesity-linked disorders appear in obese children prior to puberty; these disorders can be improved by decreasing BMI. Anthropometric parameters, insulin resistance status, and quantification of adipose tissue biomarkers can help to diagnose complications associated with the metabolic syndrom.

P2-d1-746 Fat Metabolism, Obesity 7

Timing of puberty and physical growth in obese children: a longitudinal study in boys and girls

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Background: There is emerging evidence suggesting that childhood obesity may influence the timing of puberty and growth patterns. However, there are scant and controversial data in this field.
Objective and hypotheses: To assess whether puberty and physical growth vary in obese when compared to normal-weight children.

Methods: 100 obese pre-pubertal children (44 boys; mean age (±SD): 8.8±0.6 years; BMI SDS: 2.69±0.49) were compared to 55 normal-weight controls (27 boys; 8.9±0.5 years; BMI SDS: 0.16±0.65). All study participants were followed prospectively and data collected at 4 specific time points (pre-puberty, onset of puberty, late puberty and adult height) were analyzed. At each study visit, height, weight, BMI and pubertal stage were assessed.
Results: Obese children entered puberty and achieved later stages of puberty earlier than controls (onset of puberty: 10.7±1.2 vs 11.2±1.2 years, p=0.012; late puberty: 12.3±1.2 vs 13.4±1.4 years, p< 0.001). Pre-pubertal BMI SDS was inversely associated with both age at the onset of puberty (β=-0.506, p< 0.001) and age at late puberty (β=-0.514, p< 0.001).
Height SDS was significantly higher in obese than in normal weight children at the first study visit (pre-puberty) (1.08±0.69 vs 0.31±0.68, p< 0.001) as well as at the onset of puberty (0.69±0.74 vs 0.38±0.48, p=0.008), whereas there was no statistically significant difference in height SDS at late puberty (0.41±0.72 vs 0.43±0.52, p=0.78) and at achievement of adult height (0.37±0.61 vs 0.35±0.54, p=0.85). Obese children also showed an earlier age at peak height velocity (APHV) (11.9±1.1 vs 12.7±0.9 years, p< 0.001) and a lower peak height velocity (PHV) (7.6±1.7 vs 8.6±1.6 cm/year, p< 0.001). Prepubertal BMI SDS was inversely and significantly associated with APHV (β=-0.52, p< 0.001) and PHV (β=-0.32, p< 0.001).
Conclusions: Obese boys and girls presented an early onset of puberty and completion of puberty and an impaired height gain during puberty.

P2-d1-747 Fat Metabolism, Obesity 7

Circadian rhythm of NAMPT, metabolic parameters and hormone levels and the impact of obesity and physical exercise

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Background: The adipocytokine Nampt is known to be elevated in type 2 diabetes and obesity and may be a mediator linking obesity, inflammation and insulin resistance.
Objective and hypotheses: We aimed to evaluate whether there is a circadian rhythm of Nampt and if this, metabolic parameters and hormones are altered in obese subjects.
Material and methods: 32 young adults (aged 25.23 ± 4.7) including 14 lean (BMI 20.19 ± 3.70), 14 obese (38.23 ± 5.88) and 4 overweight (25.49 ± 0.82) subjects participated in a 29h session, including a resting period of 8 hours at night and standardized meals. All subjects were healthy and free of medications. Nampt serum concentrations and metabolic and hormone parameters were measured in 1h intervals. An OGTT and physical exercise session was performed.
Results: We observed a physiological diurnal rhythm of cortisol and no differences between the two genders. Nampt serum levels were significantly higher in the obese (2.05±0.48ng/ml) compared to the lean (0.84±0.19ng/ml). We found elevated fluctuations and high variations of Nampt serum concentrations in obese subjects. Physical exercise has lead to an increase of Nampt and cortisol serum levels in both groups. During an OGTT cortisol levels decreased and Nampt levels were not influenced. Metabolic parameters were more deranged in the obese males. We found higher serum concentrations of glucose, insulin, proinsulin, c-peptide and triglycerides. Obese males had significant lower levels of testosterone, DHEAS, SHBG and fT4. The circadian rhythm of testosterone was impaired in the obese group and showed no adequate rise as you would expect at that age, hence it was comparable to that of elderly males.
Conclusions: Diurnal Nampt serum levels are approximately twice as high in obese compared to lean controls and are elevated after physical exercise. A circadian rhythm of Nampt was found for almost half of the subjects. Obese females seem to be metabolically healthier than obese males.

P2-d1-748 Fat Metabolism, Obesity 7

Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis

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Background: The rising prevalence of obesity in children has been linked in part to the consumption of sugar-sweetened drinks. Our aim was to examine this relation.
Methods: We enrolled 500 ethnically diverse schoolchildren (age 11·7 years, SD 0·8) from public schools in four provinance communities, and studied them prospectively for 19 months from October, 2009, to May, 2012. We examined the association between baseline and change in consumption of sugar-sweetened drinks (the independent variables), and difference in measures of obesity, with linear and logistic regression analyses adjusted for potentially confounding variables and clustering of results within schools.
Results: For each additional serving of sugar-sweetened drink consumed, both body mass index (BMI) (mean 0·24 kg/m2; 95% CI 0·10-0·39; p=0·03) and frequency of obesity (odds ratio 1·60; 95% CI 1·14-2·24; p=0·02) increased after adjustment for anthropometric, demographic, dietary, and lifestyle variables. Baseline consumption of sugar-sweetened drinks was also independently associated with change in BMI (mean 0·18 kg/m2 for each daily serving; 95% CI 0·09-0·27; p=0·02).
Conclusions: Consumption of sugar-sweetened drinks is associated with obesity in children.

P2-d1-749 Fat Metabolism, Obesity 7

Impairment of inflammatory markers in children and adolescents with familial hypercholesterolaemia

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Background: Familial hypercholesterolemia (FH) is an independent risk factor for premature cardiovascular disease (CVD).
Objective: To longitudinally evaluate serum markers of inflammation and endothelial activation (sM) in children with FH and healthy controls.
Methods: We determined lipid profile, intercellular cell adhesion molecule-1 (ICAM-1), endogenous secretory receptor of advanced glycation end products (esRAGE) and endothelin (ET-1) in 20 children and adolescents with FH (9.25 ± 3.66 yr) and 24 controls (C) (7.74 ±3.61 yr) at time 0 and after a mean follow-up of 92 months (time 1).
Results: At time 0, no differences in sM levels were documented between FH patients and C. After TLCs diet (time 1), ICAM-1 and esRAGE levels significantly increased in FH patients despite an improvement of lipid profile.

	Time 0	Time 1	p
Total Cholesterol (mg/dl)	312.95 ± 35.43	264.53 ± 49.19	0.00
LDL (mg/dl)	226.35 ± 45.77	184.15 ± 46.91	0.00
ICAM-1 (ng/ml)	97.24 ± 28.08	262.65 ± 52.52	0.00
esRAGE (ng/ml)	0.24 ± 0.11	0.46 ± 0.17	0.00
ET-1 (pg/ml)	5.14 ± 5.65	3.75 ± 4.09	0.30

[FH patients]

When FH patients were categorized in relation to familial history of premature CVD, higher ICAM-1 levels were detected in patients with familial CVD+ than CVD- at time 0 (p 0.03). In FH, the variation of ICAM-1 during follow-up correlated with the reduction of CT (r 0.46, p 0.03) and LDL levels (r 0.47, p 0.03). Multivariate regression analysis identified familial CVD+ as predictive factor for ICAM-1 increase.
Conclusions: Our results demonstrated an increase of ICAM-1 and esRAGE levels, suggesting a progression of endothelial dysfunction, in asymptomatic FH children and adolescents despite a diet-induced improvement in lipid metabolism. sM may be early indicators of vascular damage and, together with familial history of premature CVD, may help clinicians in identifying children at risk before CVD develops.

P2-d1-750 Fat Metabolism, Obesity 7

More new clinic manifestations in adolescents and youths with metabolic syndrome and benefits of insulinosensitizers and antidepressants

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Background: New Metabolic Syndrome (MS) clinical manifestations are increasing. We observed frequently in adolescents with SM: acrochorda (ACR), Seborrheic Keratosis (SK), anxiety/depression (A-D), smell of rancid fat in sweat and scalp (SRF), as well as abdominal obesity (AOB) and insulin resistance (IR) are frequently associated with A-D and inappropriate eating behavior (IEB), forming a vicious cycle. In addition, Vildagliptin (VIL) which has selective action and other Insulinosensitizers (INS) Pioglitazone (PIO), Metformin (MET), are useful in adults with MS but little is known on children. Escitalopran (ESC) is a fast stabilizer of A-D, improving IEB, combined with B Complex vitamins (BCV).
Objective and hypotheses: Study in adolescents and youth the association of AOB, Hypertriglyceridemia (HTG) and IR with ACR, SK, IEB, A-D , SRF and effects of 3 different INS: PIO, VIL or MET, combined with ESC , VCB, hypocaloric diet (HCD) and aerobic exercise (EXA).
Methods: 35 men (M) and 10 women (W),15- 22 years old, with AOB: Waist Circunference (WC) 114-135 cm (M), 97-114 cm (W), IEB, HTG, ACR, SK, SRF, fasting or postprandial glucose altered (FGA) or (OGI), HOMA > 4, with the rest of laboratory and clinical examination normal, were randomly assigned to 1 of 3 branches. They were treated for 6 months, the first branch with PIO 15 mg day, 2nd with MET 500 mg and 3rd with VIL 50 mg. All followed HCD, ESC 10 mg, VCB, and a supervised EXA program of 1 hour daily.
Results: All subjects decreased AOB significantly ($p < 0.001$, *t* Test), WC: 100-112 (M), 86-100 (W). There was greater reduction of IR in those treated with VIL and MET. All subjects normalized FGA, OGI, SK, SRF and improved HTG, HOMA, IEB, A-D, stabilizing ACR.
Conclusions: AOB, SM and IR relates strongly with SRF, IEB, ACR, A-D, SK which improve with HCD, EXA, INS, suggesting hyperinsulinism as pathophysiology of these new SM manifestations. More studies could better determine promising VIL action in children with MS.

P2-d1-751 Fat Metabolism, Obesity 7

Salt intake and insulin resistance in obese children and adolescents

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Background: Excess dietary salt and caloric intake is linked not only to increased blood pressure (BP), but also to defective insulin sensitivity and impaired glucose homeostasis. Activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system as well as increased signaling through the mineralocorticoid receptor, result in increased production of reactive oxygen species and oxidative stress, which contribute to insulin resistance (IR).
Objective and hypotheses: To evaluate the influence of salt intake on BP and IR in pediatric obesity, we analyzed data from 111 obese children and adolescents (mean age 11.64 ± 3.52; z-score IMC 3.7 ± 0.99).
Methods: Subjects underwent a standard physical examination and an anthropometric evaluation. Glucose and insulin levels were measured after a 12-hour overnight fast. IR was determined using the HOMA-IR. BP was measured by an automatic device (Dinamap) and values expressed as percentiles for age, sex and height. Salt intake was calculated from 24-h urinary sodium values. Daily caloric intake was estimated by a questionnaire and the excess calculated on the basis of recommended daily intake for age and sex.
Results: The study population was made of 56 boys and 55 girls, without differences in mean age and BMI z-score. Over 80 % of participants had a 24h urinary sodium excretion indicating an intake above the upper tolerable levels. Sodium excretion was similar in boys and in girls (138 vs 120 mmol/24h, p = n.s.) Salt intake (7.61 ± 3.45 g/day) was significantly related to BMI, waist-to-height ratio, basal insulin levels and HOMA-IR ($p < 0.05$ for all) but not to systolic or diastolic values of BP or caloric excess *per se*.
Conclusions: Salt intake appears to be related to IR in obese children and adolescents. Our results confirm the opportunity of the reduction of salt intake in the management of obesity to improve insulin sensitivity and glucose homeostasis.

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Orlistat prescribing in Scottish children and adolescents and the potential of treatment discontinuation as a signal for adverse drug reactions

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Background: Paediatric obesity is a growing problem, hence the demand for therapeutic treatments. Orlistat is the only anti-obesity drug licensed for use in adults in the United Kingdom and is consequently being used in children despite limited information on its safety profile.
Objective: To assess the use of routinely acquired healthcare data to identify orlistat utilisation, and discontinuation as a signal for possible adverse drug reactions (ADRs) in children.
Methods: The Primary Care Clinical Informatics Unit (PCCIU) database and national dispensing Prescribing Information System (PIS) were used to assess orlistat prescribing, discontinuation and possible ADRs in children < 19 years of age. Discontinuation was defined as a cessation of prescription: < 1 month; 1-3 months; >4months of first prescription. Possible reasons for discontinuation were sought by: examining diagnoses in the PCCIU dataset; linking PIS data to hospital admission diagnoses recorded in the Scottish Morbidity Record (SMR01).
Results: Orlistat prescribing and utilisation patterns were similar for the PCCIU and PIS databases. Approximately 80% of patients discontinued treatment within 3 months. Respiratory (10.1%), genitourinary (8.9%) and obstetric (5.1%) symptoms were most commonly recorded in the PCCIU database at the time of discontinuation. Linkage of PIS data with SMR01 identified obstetric and gastrointestinal symptoms as the most common reasons for hospital admission. Spontaneous miscarriage was recorded in approximately 1.5% of exposed patients in both databases.
Conclusions: Healthcare database can be used to assess drug utilisation and possible reasons for treatment discontinuation in children. Orlistat is not well tolerated in children, a finding similar to that reported by others (2). The miscarriage rate identified is similar to reported teenage miscarriage rate and therefore unlikely a result of orlistat use (3). No severe ADRs were associated with the use of orlistat.

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Short-term intervention improves cardiorespiratory fitness, glucose metabolism and lipid profile in obese children and adolescents

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Background: Childhood obesity can impair glucose metabolism, the cardiovascular risk factors as well as fitness and quality of life. Studies analyzing physical performance in relation to glucose and lipid metabolism after obesity intervention in youth are rare.
Objective: We aimed to evaluate short-term effects of inpatient obesity intervention in youth focusing on cardiorespiratory fitness and metabolic factors.

Methods: A total of 58 obese children and adolescents (age 7-17 years, mean BMI SDS 2.41 +/- 0.41) participated in an inpatient intervention of 4 to 6 weeks. The program combined nutritional education, physical exercise and cognitive behavioral therapy. Before and after the intervention anthropometric data and metabolic state including oral glucose tolerance were evaluated. Coordinative capacity, fitness, strength and flexibility were tested using selected test items. Cardiorespiratory capacity was assessed by a shuttle run test.
Results: Participants achieved significant weight loss completing the intervention (mean Δ BMI SDS -0.26 +/- 0.1). Significant improvement was found in motor performance except for flexibility. Subjects reached average motor fitness of children in Germany (SDS 0,04 +/- 0.62). They ran more shuttles (Δ -6.7 +/- 9.44), reached higher velocity (Δ -0.62 +/- 0,77 km/h) and improved VO2 max. (Δ -2.1 +/- 2,64 ml/kg/min) significantly after the intervention. In oral glucose tolerance test significant reduction of mean glucose and peak insulin were detected. Baseline values for insulin and glucose remained unchanged. Insulin resistance (Peak insulin >700 pmol/l) was present in 35 subjects before but only in 15 subjects after the intervention.
Conclusions: Early and intensive obesity intervention in children and adolescents was effective not only in significant weight-loss but also improved physical capacity and metabolic parameters. The advancement in motor performance may motivate obese children to persue physical activity in daily life.

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Associations between weight variation, thyroid function and other metabolic variables in obese children

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Background: Serum TSH is frequently elevated in obese children, which may be related to lipids and glucose metabolism dysfunction. However, clinical relevance of these associations remains unclear.
Objective: To analyse the influence of BMI-SDS and TSH variations in other metabolic variables.
Methods: Retrospective longitudinal study with data collected at baseline and one year after lifestyle intervention in obese children referred to our clinic. Demographic, anthropometric and metabolic variables were analyzed. For statistical analysis of post-intervention status, three groups were considered according to BMI-SDS variations: ≤-0,5 (significant weigh loss); 0,5-0 (weight loss) and >0 (weight gain). A p-value ≤ 0.05 was considered for statistical significance.
Results: From the 348 initially analyzed children, 100 had data at baseline and one year after intervention. Weight reduction was verified in 70%, but significant loss was present in only 22,8% of cases. Decreases in both TSH and BMI-SDS were associated with decreases in HOMA-IR and these effects were independent (p=0,002 and p=0,004, respectively). There was no relationship between TSH and BMI-SDS variations. A relation between BMI-SDS and lipids variations was found, exception made to total cholesterol [LDL (p< 0,001), HDL (p=0,024) and triglycerides (p=0,025)]. TSH variation was related to total cholesterol variation (p=0,023) as well as to LDL (p=0,024). In the significant weight loss group there was a significant decrease in the HOMA-IR (p=0,02) and LDL (p=0,002), compared to the weight gain group. There were no significant differences among these groups for the other variables.
Conclusions: There was no association between weight and TSH values variations throughout the intervention. Hyperthyrotropinemia seemed to exacerbate insulin resistance in obese children. Weight loss with non-pharmacological measures alone, improved the metabolic profile of our obese children, but no TSH decrease was observed.

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Melatonin in obese pubertal patients: correlation with metabolic syndrome and other cardiovascular risk factors

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Background: Alterations of some neuroendocrine factors in obesity and metabolic syndrome in pubertal subjects remain controversial.
Objective: To correlate melatonin secretion with different components of metabolic syndrome and other cardiovascular risk factors.
Patients and methods: We evaluated 76 obese pubertal patients, classified as G1 (Tanner II and III): 15 males; 19 females and G2 (Tanner IV and V): 15 males; 27 females, with BMI >2SDS. Metabolic syndrome was defined using Cook criteria. We measured urinary *6-sulfatoxymelatonin* (6-SM) (radioimmunoassay, Stockgrand Ltd, Guildford, UK) in nocturnal (6-SMn: 6PM to 8AM) and diurnal samples (6-SMd: 8AM to 6PM). Levels of 6-SM were expressed as µg excreted per time interval and delta 6-SM as the difference between nighttime and daytime values. Insulin was measured by ECLIA (cobas E411, Roche Diagnostics GmbH. Mannheim).Results (median):

	6-SMn (µg)	6-SMd (µg)	Δ 6-SM (µg)	Insulin (µU/L)	Glucose (mg/dl)	T-Chol (mg/dl)	HDL (mg/dl)	Triglyc (mg/dl)	Uric Acid (mg/dl)
Males G1	0.94	0.45	0.48	17.3	94.0	166.0	46.0	87.0	4.0
Males G2	1.25	0.46#	0.25^	21.1	91.5	165.0#	34.0	131.0	5.5^
Females G1	1.45	0.83	0.61	21.0	92.0	171.0	38.0	119.0	4.8
Females G2	0.70*	0.45	0.31	21.4*	92.0	154.0	40.0	83.0	4.7

[table 1]

* Rs=0.42, p=0.0274; #Rs= -0.58, p=0.0245; ^Rs=0.89, p=0.0476 (Spearman Rank order correlation) No associations were found between melatonin secretion and the presence of abdominal obesity, hypertension, metabolic syndrome or family history of cardiovascular risk in either gender.
Conclusions: Associations between melatonin secretion and some alterations of metabolic biochemical parameters were only found in Tanner stages IV and V and they were different in both genders.Our results suggest that some neuroendocrine abnormalities associated with obesity and metabolic syndrome have sexual dimorphism and that they would become apparent in the final stages of puberty.

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Evaluation of waist-to-height ratio as an indicator of cardio-metabolic risk in 6-10-year-old children

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Background: Childhood obesity is a worldwide problem and followed by increased risk of cardiovascular and metabolic disturbances.
Objective and hypotheses: This study aims to compare the performances of waist-to-height ratio (WHtR) and the 2007 World Health Organization (WHO) body mass index (BMI) in screening the cardio metabolic and inflammatory disturbances in 6-10-year-old children.
Methods: A cross-sectional study was undertaken including 175 subjects, selected from the Reference Center for the Treatment of Children and Adolescents. The subjects were classified according to 2007 WHO standard as non-obese (BMI z score > -1 and < 1) or overweight/obese (BMI z score ≥ 1). The analyzed variables were systolic (SBP) and diastolic blood pressure

(DBP), fasting glycemia, low (LDL) and high-density lipoproteins (HDL), triglyceride (TG), Homeostatic Model Assessment - Insulin Resistance (HOMA-IR), leukocyte count and ultrasensitive C-reactive protein (CRP).
Results: There were correlations between WHtR and BMI *z* score ($r = 0.88$, $p < 0.0001$), SBP ($r = 0.51$, $p < 0.0001$), DBP ($r = 0.49$, $p < 0.0001$), LDL ($r = 0.25$, $p < 0.0008$, HDL ($r = -0.28$, $p < 0.0002$), TG ($r = 0.26$, $p < 0.0006$), HOMA-IR ($r = 0.83$, $p < 0.0001$) and CRP ($r = 0.51$, $p < 0.0001$). The WHtR area under the curve was equivalent to that of the BMI in the diagnosis of all cardio metabolic variables. The WHtR cut-off value of > 0.47 was sensitive for screening insulin resistance and any one of the cardio metabolic disturbances.
Conclusions: The WHtR was as sensitive as the 2007 WHO BMI in screening cardio metabolic and inflammatory risk in 6-10-year-old children, even in the normal-weight ones. The message "keep your waist to less than half your height" is effective in preventing the cardio metabolic disturbances in primary pediatric care.

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Cardio-metabolic risk profile in Chilean adolescents of mid-low socioeconomic level: association with sex and obesity

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Background: Obese children and adolescent are more likely to become obese adults. Several studies demonstrate that early onset obesity increase cardiovascular and metabolic risk (CVMR) in adulthood. Over the past 20 years, obesity has remarkably increased in Chilean children and adolescents.
Aim: We analyzed the cardiovascular and metabolic profile of 16.8±0.2 adolescents to test for differences according to the number of CVMR factors. We tested for association according to sex and obesity.
Methods: Data from 679 Chilean adolescents of Mid-low SES from a longitudinal follow-up were used. BMI (Kg/cm^2), waist circumference (WC), triglycerides (TG), total cholesterol (TChol), insulin (Ins), and glucose (Gli) were measured. Obesity was diagnosed according to CDC/NCHS 2000. Abdominal obesity and BP, fasting hyperglycaemia and HDL-Chol alteration were diagnosed based on Cook criteria. HOMA-IR was calculated; values ≥3.3 according to national standards were considered insulin resistance (IR). Chi2 test (Pearson) was performed to study the association of CVM risk with sex and obesity. Variance analysis and Bonferroni test were used for comparison of means. A $p < 0.05$ denoted statistical significance.
Results: About 80% of adolescents in the sample had at least one risk factor, and 9% had three or more. CVMR factors were more prevalent among males ($p < 0.001$) and obese individuals ($p < 0.001$). In addition, early onset obesity (at 5 and 10 years) was positive and significantly associated with CVM risk in adolescence. Mean values of BMI z-score, WC, Syst-BP, Diast-BP, TG, HDL-Chol, and HOMA-IR significantly increase ($p < 0.001$) with the number of CVMR factors.
Conclusions: In our sample, sex and early and current obesity were associated with higher CVM risk. Having three or more CVM risk factors entailed remarkably higher values of BMI z-score, WC, Syst-BP, Diast-BP, TG, HDL-Chol, and HOMA-IR.
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Abstract has been withdrawn

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Trends in lipid profile components and lifestyle factors in Korean adolescents; the KNHANES study 1998-2010

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Background: To determine time trends in lipid profile components and associated life style factors in Korean adolescents.
Methods: Using the data from Korean Nutrition Health and Nutrition Examination Survey (KNHANES) in 1998 and 2010, a total of 1107 boys and 987 girls aged 10-18 years, were evaluated with age-adjusted analyses. Diet, smoking, alcohol drinking and physical activity information were collected and anthropometric parameters, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride were measured.
Results: Between 1998 and 2010, the prevalence of obesity was significantly increased in boys, whereas no changes were observed in girls. Among lipid profile components, mean LDL-cholesterol in boys (87.5 mg/dL in 1998, 83.6 mg/dL in 2010; $P=0.019$) and mean triglycerides in girls (90.8 mg/dL in 1998, 85.8 mg/dL in 2010; $P=0.020$) were significantly decreased. There were no significant changes in the prevalence of dyslipidemia in both genders. During the study period, the prevalence of breakfast skipping was decreased, whereas the prevalence of regular exercise was increased in both genders. Daily total energy intake did not change between 1998 and 2010. In multivariate logistic regression analyses, breakfast skipping increased risk (odds ratio) for hyper-LDL-cholesterolemia (5.77), and regular exercise decreased risk for hypo-HDL-cholesterolemia (0.40) in boys. In girls, breakfast skipping increased risk for hypertriglyceridemia (2.27).
Conclusions: Even though the prevalence of obesity in boys was increased, decrease in breakfast skipping and increase in regular exercise may contribute to favorable trend of lipid profile in adolescents.

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Metabolic syndrome criteria predicting non-alcoholic fatty liver disease: comparison of two methods

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Background: Childhood obesity is increasing and is associated with several risk factors referred to as the metabolic syndrome (MS).The risk factors for non alcoholic fatty liver disease (NAFLD) are the main features of MS .Recent reports suggested that NAFLD may not only be a liver disease, but also an early mediator of MS in children .NAFLD is not a component of the diagnostic criteria for MS, however, the development of NAFLD has some common mechanisms with the development of MS, as they share the pathophysiologic basis of insulin resistance.
Objective: The aim of this study was to identify which metabolic syndrome criteria (WHO and IDF) better reflect the presence of NAFLD and to determine the prevalence of MS and NAFLD.
Methods: Two hundred and seventeen obese children and adolescents, 8-15 years of age (body mass index> 95 p) were included in the study. Anthropometric measurements, blood pressure measurements, an oral glucose tolerance test and lipid profile were measured. MS was diagnosed according to WHO and IDF criteria. NAFLD risk ratio was assessed according to the two MS criteria by logistic regression analysis.
Results: The prevalence of MS according to the IDF criteria was 43.3%, and according to WHO criteria it was 55.2%. NAFLD prevalence in the metabolic syndrome group according to IDF criteria was 25.5% and this was statistically significant ($p = 0.007$). The prevalence of NAFLD was 20.8% in the group

with MS according to WHO criteria and this was not a statistically significant difference (p = 0.15). NAFLD hazard ratios were 7.06 (95% CI 1.29 to 5.50) in the MS group according to IDF criteria and 2.02 (95% CI 0.81 to 3.53) in the group with metabolic syndrome according to WHO criteria. IDF criteria were found to have a higher odds ratio.
Conclusion: The prevalence of MS depends on the diagnostic criteria used. IDF criteria reflect the best measure for the presence of NAFLD. NAFLD might be considered in diagnostic criterias for MS.

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Polycystic ovary syndrome treatment during adolescence: improvement of clinical and metabolic parameters with metformin versus oestroprogestins and antiandrogens

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Background: Polycystic Ovary Syndrome(PCOS) is the most common endocrine disorder in young women. It's characterized by clinical or biochemical hyperandrogenism and menstrual dysfunction (chronic oligo-anovulation). It is often associated with overweight or obesity and with insulin resistance and hyperinsulinism.
Aim of the study: To assess the efficacy of metformin (MET) in improving clinical (oligo/amenorrea, hirsutism/acne and BMI) and metabolic parameters (insulin resistance and lipidic profile) in adolescents with PCOS compared to oestroprogestins (EP) treatment. Secondarily to evaluate side effects associated with different treatments.
Materials and methods: 72 adolescents with PCOS (mean age 15.55 ± 2.06, range 12.49 to 22.39) among girls afferent to Endocrinology Unit in Pediatric Hospital Bambino Gesù. PCOS was diagnosed on the basis of the combination of changes in the ovarian cycle/abnormalities at ultrasound evaluation with clinical (hirsutism/acne) and/or biochemical hyperandrogenism. We conducted a prospective cohort study of 24 months. Patients were divided into three treatment groups:
1. MET group (15 patients)
2. MET-EP group (19 patients)
3. EP group (38 patients).
Results and discussion: MET alone was effective in improving menstrual cycle in 100% and in reducing hirsutism/acne in 76.9% and in 83 3% girls, respectively. In MET group lower levels of testosterone after 12 months of therapy and an improvement of basal insulin level and of insulin resistance -HOMA-IR-(after 24 months of therapy) were noted. Only mild gastrointestinal side effects were recorded. MET-EP group showed similar results, but worsening in lipidic profile was recorded. A significant reduction of BMI z-score was noted in MET and MET-EP.
In conclusion metformin alone for at least 6 months can be considered as the first-line therapy, the addition of oestroprogestins being considered in case of lack of clinical improvements.

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Impaired theory of mind and symptoms of autism spectrum disorder in children with Prader-Willi syndrome

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Background: Prader-Willi syndrome (PWS) is a neurogenetic developmental disorder due to a lack of expression of the Prader-Willi region of the paternally derived chromosome 15. Common clinical features of PWS include hypotonia, developmental delay, hyperphagia resulting in obesity when uncontrolled, hypogonadism, characteristic appearance and behavioral abnormalities.
Objective: In order to evaluate social cognitive functioning in children with PWS, Theory of Mind (ToM) and symptoms of Autism Spectrum Disorder were assessed.
Method: Sixty-six children with PWS aged 7 to 17 years were tested using the Theory of Mind test-R and the Diagnostic Interview for Social Communication disorders. We tested the correlation between Total ToM Standard Deviation Score (Total ToM SDS) and genetic subtype of paternal deletion or maternal uniparental disomy, and total IQ, verbal IQ and performal IQ. Prevalence and symptoms of ASD were assessed.
Results: Median (interquartile range) of total ToM SDS of those aged 7 to 17 years was -3.84 (-5.73, -1.57). Their Total ToM SDS correlated with total IQ (β= 0.629, p< 0.001, adj. R^2=0.407), in particular with verbal IQ (β= 0.524, p< 0.01, adj.R^2=0.409), but not with performal IQ (β= 0.241, p>0.05, adj. R^2=0.259). No difference in Total ToM SDS was found between children with deletion and maternal uniparental disomy (β=-0.143, p>0.05, adj.R^2=0.016). Compared to the reference group of healthy children aged 7 to 12 years, children with PWS in the same age group had a median ToM developmental delay of 4 (3-5) years.
One third of children with PWS scored positive for ASD. Children with PWS have a specific profile within the Autism Spectrum Disorder as the most prominent aberrations were focused on maladaptive behavior.
Conclusions: Our findings demonstrate a markedly reduced level of social cognitive functioning which has consequences for the approach of children with PWS, i.e. adjustment to the child's level of social cognitive functioning.

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Evaluation of early markers of risk for metabolic syndrome and vascular function in children with intrauterine growth restriction

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Background: Intrauterine growth restriction(IUGR) is considered a cardiovascular risk factor, this would result in the appearance in Metabolic Syndrome (MS).
Objective: To study the relationship between the early markers of risk of MS and assess endotelila function:EF in children with a history of IUGR.
Methods: A cross-sectional study was performed.
Population: 120 children born with low birth weight (2006-2009) from Maternity (84 were IUGR). Signed informed consent from parents was required. Anthropometric variables and biochemical parameters were: body mass index:BMI, waist circumference:WC, glucose:G, insulin:I, HOMA and QUICKI:QI, lipid profile and IGF-1. EF was assessed by plethysmography digital pulse wave before and after of reactive hyperemia maneuver. Pearson correlation coefficient was used.
Results: Birth weight and weeks and gestational age:GA were 2297.0±24 g and 37±0.2 respectively. The mean values were: G 78±1 mg/dl, I 8.25±0.7 uUI/ml, HOMA 1.6±0.1, IQ: 0.36±0.03, HDL 45±1 mg/dl, TG:86±5 mg/dl,TG/HDL 2.1±0.2 and IGF-1 165±11 ng/ml and PCR 2.0±0.5 mg/l. The presence of MS was 14%.Both BMI and WC were correlated with HOMA (0.35 p=0.003 and 0.24 p=0.03) and IQ (-0.27 p=0.03 and -0.28 p=0.01). The diastolic blood pressure (DBP) was correlated with WC (0.29 p=0.007) and BMI with systolic blood pressure (SBP p=0.02). HOMA, IQ and HDL correlated with TG (p=0.003, p=0.02 and p=0.001 respectively). IGF-1 correlated with BMI (p=0.034), WC (p=0.001), HOMA (0.22 p=0.049), IQ (-0.35 p=0.001). A positive correlation between SBP and DBP (p=0.001) was found, accompanied by a differential pressure increased (p=0.001). EF were correlated with both GA (0.55 p=0.01) and DBP (p=0,04).
Conclusions: Children with IUGR were significantly associated with early markers of risk of MS.The positive correlations observed between anthropometric variables with biochemical parameters and endothelial dysfunction, suggesting that IUGR would be potential carriers MS.

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Association of pre-pregnancy weight with weight status and classical cardiovascular factors at 4 years

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Background: Prevalence of childhood obesity is a serious public health concern. Risk for obesity in early childhood must be identified.
Objective: To analyse association of pre-pregnancy weight with BMI, adiposity and metabolic profile at 4 years.
Methods: 485 pregnant mothers (2004-2007) and 409 children from a population- based birth cohort study. We analyzed maternal BMI, BMI and the sum of four skinfold thicknesses at 4 years. Lipid profile, ALT, AST, C-Reactive Protein, glucose and insulin were determined. Insulin resistance (IR) was calculated using homeostasis model assessment for IR (HOMA-IR). Statistical analyses were conducted.
Results: 22.3% mothers were overweight (BMI 25-29.9 kg/m^2) and 8.5% obese (BMI $\geq$ 30 kg/m^2). 91 to 409 children were overweight or obese at 4 years. There are positive association among BMI at 4 years and pre-pregnancy BMI, and skinfold thicknesses (r Pearson 0.296, 0.229; p< 0.01). Table 1 shows metabolic profile at 4 years. Maternal overweight or obesity increases the risk of child overweight or obesity by 1.2 (95%CI 1.06-1.38). 18.9 % children have HOMA-IR >2.4. Overweight or obesity at 4 years increases the risk of IR by 1.19 (95%CI 1,004-1.410).

	Normal weight (n 198)	Overweight (n 38)	Obese (n 25)	p
Glucose (mg/dL)	84.9 ± 8.1	89.4 ± 7.3	88.5 ± 6.9	0.002
Total cholesterol (mg/dL)	162.1 ± 26.4	169.8 ± 28.3	176.8 ± 22.8	0.01
C-HDL (mg/dL)	56.5 ± 13.8	54.6 ± 12.2	52.7 ± 8.4	NS
C-LDL (mg/dL)	89.8 ± 23.6	99.6 ± 26.2	103.9 ± 21.9	0.004
ALT (IU/L)	16.5 ± 7.1	19.8 ± 12.5	27.9 ± 42.9	0.002
AST (IU/L)	31.2 ± 7.2	33.19 ± 12.9	36 ± 24.7	NS
CRP (mg/L)	0.5 ± 2.7	0.5 ± 1.8	0.1 ± 0.4	NS
Insulin (µU/mL)	5.7 ± 7.1	9.1 ± 10.9	8.8 ± 11.4	0.03
HOMA	1.3 ± 1.7	2.1 ± 2.7	2.0 ± 2.7	0.023

[Table 1 Metabolic profile of the children at 4]

Conclusions: High prevalence of overweight and obesity maternal and at 4 years was detected. Correlation between them was found. An adverse metabolic profile is associated with overweight and obesity in children of 4 years. Childhood obesity prevention must be started from pregnancy and infancy.

P2-d3-765 Fat Metabolism, Obesity 9

Serum apelin12 levels in obese youngsters with altered glucose homeostasis-insulin resistance

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Background: Although apelin levels are reported to be associated to glucose homeostasis and obesity in adults, in obese youngsters the results are scarce and controversial.
Objective and hypotheses: To investigate serum apelin levels in obese youngsters with impaired metabolism(IGT), including insulin resistance.
Methods: Ninety obese individuals(45 prepubertal) and 90 leans matched for age-gender were enrolled. Glucose homeostasis was assessed by oral glucose tolerance test and serum apelin levels were determined by enzyme immunoassay.

Results: Table 1

	Obese (n=90)	Obese prepubertal (n=45)	Obese pubertal (n=45)	Controls (n=90)	Controls prepubertal (n=45)	Controls pubertal (n=45)
Age (years)	11.6 (2.6-16.5)	9.3 (2.6-12.05)	13.06 (11.48-16.5)	11.92 (2.8-16.8)	8.4 (3.3-11.9)	12.5 (11.2-17.8)
Gender	56F/34M			47F/43M		
BMI (kg/m2)	28.20 (17.70-46.60)	26.10)17.70-41.95) 30.10(24.70-46.60)		18.50 (13.50-26.10)	17.10 (13.57-21.05)	20.04 (14.30-26.10)
HOMA-IR	2.90 (0.77-14.60)	3.06 (0.77-7.63)	2.70 (1.20-14.60)	1.70 (0.49-3.02)	1.49 (0.61-2.55)	1.82 (0.49-3.02)
Impaired Glucose metabolism	64/90	33/45	31/45	-	-	-
Normal Glucose Metabolism	26/90	12/45	14/45	-	-	-
Apelin (ng/ml)	1.64(0.65-3.99)	1.68 (0.67-3.99)	1.55 (0.65-3.80)	2.21 (0.61-4.74)	2.31 (0.61-4.20)	2.02 (0.71-4.74)

[Characteristics and laboratory data]

Obese girls had lower apelin levels compared to controls (1.84 (0.65-3.9) vs 2.38 (0.62-4.74), p=0.024), but this difference did not exist in puberty (prepubertal girls: 1.8 (0.67-3.9) vs 2.42 (0.62-4.16), p=0.018/ pubertal girls: 1.9 (0.68-3.8) vs 2.25 (0.82-4.7), p=0.362). Prediabetic obese youngsters had significantly lower apelin levels compared to healthy controls (1.56 (0.65-3.87) vs 2.2 (0.61-4.74), p=0.011), particularly those prediabetics with insulin resistance [1.39 (0.60-3.80)].
Conclusions: Obese youngsters have lower apelin levels in comparison to lean individuals, especially prepubertal girls. Only prediabetic obese youngsters have significantly lower apelin levels compared to healthy controls, since this difference does not exist in obese with normal glucose metabolism. The fact that the majority of prediabetic obese individuals are insulin resistant indicates a strong link between apelin and glucose-insulin homeostasis, even from childhood.

P2-d3-766 Fat Metabolism, Obesity 9

The relationship between carotid-intima thickness and fibrin monomers in obese children

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Background: Obesity has been demonstrated to be associated with cardiovascular risk factors, such as hypertension, dyslipidemia, impaired glucose metabolism in children and adolescents. Early development of insulin resistance and impaired oxidant antioxidant status may lead to endothelial dysfunction and increased carotid intima-media thickness (IMT) even in childhood.
Objective and hypotheses: To investigate the relationship between carotid IMT and fibrin monomers in childhood obesity.
Methods: 74 obese children (mean age 12,7±2,4) and 31 healthy children (mean age 13,4±2,3) with normal weight were included in the study. BMI SDS, waist/hip ratio, systolic and diastolic blood pressure values of all participants were recorded. Fasting blood glucose, insulin, lipid profile, homosistein, fibrin monomer, lipoprotein(a) and D-dimer levels of obese children were compared with healthy controls. The carotid IMT of all subjects were measured by high resolution ultrasonography.
Results: Obese children had higher levels of total cholesterol and insulin compared to healthy subjects (p< 0,013 and p< 0,002). Left carotid IMT was significantly higher in obese children compared to controls (0.46 ± 0.07 vs. 0.44 ±0.04 mm, p: 0,044). In addition left carotid IMT was greater than right carotid IMT in obese children (p:0,016). There was no influence of puberty or sex on carotid IMT. Right carotid IMT was greater in obese children with lower fibrin monomer levels. In obese children there was a positive correlation between IMT and lipoprotein(a) (p:0,009) and a negative correlation between IMT and fibrin monomers (p:0,033).

Conclusions: Left carotid IMT was significantly higher in obese children compared to controls. An inverse relationship between carotid IMT and fibrin monomers, a marker of thrombosis was documented in obese children.

P2-d3-767 Fat Metabolism, Obesity 9

16p11.2 deletion accounting for early-onset morbid obesity and intellectual disability in two sisters

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Background: Cohort studies have identified 16p11.2 deletions in some individuals with severe early-onset obesity, exaggerated insulin resistance and intellectual disability. Information relating to 'typical' clinical phenotype is limited.
Objective: We report two sisters, both recently identified as having 16p11.2 deletions, as an opportunity to describe phenotypic features of this condition. Case reports:Two sisters were referred for assessment of severe early-onset obesity (ages 10yrs and 13yrs, with Body Mass Indices 43.1kg/m^2 and BMI 41.2kg/m^2). Both had longstanding obesity, hyperphagia, and moderate intellectual disability with the older sister diagnosed with attention deficit hyperactivity disorder and oppositional defiance disorder. Both were of a similar stocky build with pronounced facial and submandibular subcutaneous fat, as well as extensive acanthosis nigricans. Their mother underwent bariatric surgery in 1985 but had persistent severe obesity despite this. The older sister was diagnosed with Type 2 diabetes mellitus at presentation, while the younger only had evidence of hyperinsulinaemia. Both had persistent hypertension (now well controlled on lisinopril) as well as evidence of non-alcoholic fatty liver disease, but lipid profiles in both children have always been normal. The younger child also had severe obstructive sleep apnoea requiring continuous positive airway pressure (CPAP) at night. Despite intensive follow up from our Weight Management clinic both girls continue to relentlessly gain weight and are being considered for early bariatric surgery.
Results: Micro-array analysis in both siblings revealed a deletion of 16p11.2 affecting the SH2B1 gene. Genetic analysis is pending from their parents.
Conclusion: The clustering of severe, early-onset obesity and intellectual disability, along with unusual phenotypic features and the early appearance of comorbidities, should prompt the clinician to specifically investigate for 16p11.2 deletions.

P2-d3-768 Fat Metabolism, Obesity 9

Maternal BMI predicts therapy outcome in obese children independent of the presence of metabolic syndrome: results of a national evaluation study of multiprofessional group programs

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Background: Multiprofessional family-based behavioural interventions in obese children address modifications of diet and activity and may improve adiposity and co-morbidities even more, if specific predictors allow for targeting therapy. It is questioned, whether the presence of a cluster of co-morbidities and abdominal obesity labelled as metabolic syndrome (MetS) alters the effects of obesity therapy.
Objective: The effects of obesity therapy, measured as decrease in Body mass index-standard deviation score (BMI-SDS), are reduced in children with MetS and/or predicted by BMI of parents or age or BMI at start.
Methods: Before therapy and at 1 year, longitudinal data of 378 children (12.2±2.3 years) of an on-going national multicentre cohort study of structured therapy programs were analysed: BMI of parents; BMI-SDS; waist circumference/height ratio (WcfHt), blood pressure (BP), HDL-cholesterol, triglycerides, glucose at fast and 2h after oral glucose load, abnormities in 3 co-morbidities defining MetS.
Results: Although 79% of children were extremely obese (BMI >Percentile P.99.5), BMI-SDS decreased by 0.2±0.4, p< 0.0001 at 1 year. MetS was present in 36% of children and decreased during therapy, as BP (p< 0.05) did. MetS and biochemical parameters were not associated with changes of BMI-SDS, but age < 12 years and BMI < P.99.5 predicted lower BMI-SDS after 1 year. Only 31% of mothers and 23% of fathers had a normal BMI. BMI of mothers (r=0.3, p< 0.0001), but not of fathers, was correlated with BMISDS of the child. A high maternal BMI predicted an increase in the child's BMI after therapy (r=0.13, p< 0.05).
Conclusion: Multiprofessional group therapy significantly improves adiposity and co-morbidities of obese children, independent of the presence of metabolic syndrome. The association of maternal BMI with the child's adiposity points out the importance of psychosocial environment, making the involvement of parents in the therapy of obese children indispensable.

P2-d3-769 Fat Metabolism, Obesity 9

Weight status and risk behaviours in urban Bulgarian preschool children (2009-2013)

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Background: The increased prevalence of early obesity has led to the need of identifying and adressing particular risk behaviours at preschool age.
Objective and hypotheses: To determine the incidence of overweight (OW) and general and abdominal obesity in preschoolers and their trends from 2009 to 2013, as well as to evaluate some risk behaviours and their changes for the 4 year period.
Methods: Height, weight and waist circumference (WC) were measured in 117 children aged 4.53 ± 0.29 years attending urban kindergartens. BMI was calculated and compared with the IOTF references for the corresponding age and sex. The comparison was made with a group of 189 kindergarten children of the same age (4.58 ± 0.31 years), measured with the same methodology in 2009. A questionnaire was filled in by the parents.
Results: There is a significant drop in WC - 51.51±5.17 cm to 50.28±3.22 cm (p=0.022), without gender differences. In 2009 OW/obese were 12.7% of the children vs. 19.7% in 2013 (p=0.01). There is a decrease in the proportion of obese children (from 4.2% to 0.9%, p< 0.001) and an increase in those who are overweight from 8.5% to 18.8%, (p< 0.001), more pronounced among boys. In 2009 14.8% of the parents thought their children drunk too much soft drinks, in 2013 2.1% of parents reported soft drink consumption of 4-6 cups per day. During the 4 year period TV viewing time increased 4 times (p< 0.001), and PC time increased almost 5 fold (p< 0.001). Breastfeeding raised from duration of 4.40±3.89 to 6.79±6.02 months (p< 0.001).
Conclusions: The increasing rate of overweight children who represent the recruitment pool for future obesity requires serious consideration for the prevention of obesity. Increased sedentary behavior was identified as a candidate target for school-based and family-based interventions among urban kindergarten children.

P2-d3-770 Fat Metabolism, Obesity 9

Evaluation of serum chemerin levels in childhood obesity

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Objective: Chemerin is a novel adipokine which plays an important role in adipocyte differentation and metabolic stability at adipose tissue. A great many studies has been search out relationship between chemerin and metabolic syndrome, type II diabetes mellitus, hepatosteatosis, atherosclerosis in adults.We set out to evaluate serum chemerin levels in obese children and investigate its role in obesity associated diseases.

Population and methods: Anthropometric measurements and serum analyses were done for body mass index, fasting chemerin, insülin, glucose, triglyseride, HDL and LDL cholesterol, aminotransferases in 60 obesechildren at 7-16 age. Blood pressure measurement and abdomina lultrasonography were used for evaluation of hypertension and hepatosteatosis. As for that 30 non-obese healthy children at 7-16 age only antropometric and blood pressure measurements, fasting serum chemerin, glucose and aminotransferase levels were performed.
Results: Obese children had significantly higher serum chemerin levels than healthy controls (229.72±69.90ng/ml vs101.27±22.17ng/ml; p< 0,01). In obese children, chemerin levels were not correlated with any other variable. When both obese and healthy children were estimated, chemerin levels were correlated with age (r = 0.30), body weight (r =0.62), height (r = 0.32), BMI-SDS (r = 0.64), aminotransferase levels (r = 0.36 for AST and 0.27 for ALT), systolic and diastolic blood pressure (r = 0.45 and 0.34).
Conclusion: This study suggests that serum chemerin levels are elevated in obese children. Nevertheless relationship between chemerin and obesity associated diseases is not demonstrated in children yet.

P2-d3-771 Fat Metabolism, Obesity 9

A case of rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation: ROHHAD syndrome

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Background: Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD) is a rare disorder that mimics both common obesity and genetic obesity syndromes along with several endocrine disorders during early childhood.
Objective: We aim to present the clinical features, laboratory and imaging results of a patient with ROHHAD syndrome.
Methods: In this case report, we describe a 6 year old girl who was admitted to our emergency department with blurring of consciousness, recurrent episodes of high fever, and was suspected to have ROHHAD syndrome due to her rapid-onset obesity, hypothalamic dysfunction and alveolar hypoventilation.
Results: Her laboratory work-up was significant for hypercarbia (pH: 7.33, PCO_2: 53 mmHg, HCO_3: 27 meq/L) hypernatremia (serum Na: 152 meq/L, simultaneous plasma osmolality: 313 mosmol/kg, urinary osmolality: 286 mosmol/kg, anti-diuretic hormone level: < 0.5 pg/mL (low), low IGF-1 level: < 25 ng/mL, suppressed response to GH stimulation tests (peak GH response: 0.9 ng/mL) hyperprolactinemia (serum prolactin: 89 ng/mL). Hypernatremia responded well to low-dose oral desmopressin acetate. Hypoventilation responded to minimal ventilatory support. Cranial and dynamic sella MRI yielded normal findings. Abdominal and thoracal MRI were performed to demonstrate a possible accompanying neural crest tumor and it provided an asymptomatic ~3 cm mass in the thoracal region, which turned out to be a benign hamartomatous tissue with proliferating neural elements.
Conclusions: ROHHAD Syndrome should be considered in the differential diagnosis of rapid-onset obesity owing to its association with hypothalamo-hypophysial dysfunction and alveolar hypoventilation. Owing to the wide spectrum of clinical phenotypes with respect to the severity of presentation, a high index of suspicion is required.

P2-d3-772 Fat Metabolism, Obesity 9

Association between trace element urinary profile and body mass index in a representative adolescent population

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Background: Altered micronutrient and environmental pollutant status is implicated in the development of obesity and its complications.
Objective and hypotheses: To correlate urinary concentrations of selenium (Se), chrome (Cr), cadmium (Cd), manganese (Mn), copper (Cu), Zinc (Zn), lead (Pb) and arsen (As)) with nutritional status in a representative adolescent population.
Methods: 217 15-years old girls and 241 15-years old boys were included in the study on the occasion of a routine medical examination. Overweight and obesity were defined according to WHO and IOTF criteria for age and gender. First morning urinary samples were collected and stored at -20 °C until analysed. Urinary concentrations of trace elements were determined by inductively coupled plasma mass spectrometry (ICP-MS).
Spearman correlation analysis, Mann-Whitney test and Kruskal-Wallis test were used when appropriate.
Results: Concentrations (mean ± SEM) of trace elements were: Se (11.1±0.2), Cr (2.5±0.1), Cd (0.115±0.004), Mn (0.36±0.03), Cu (7.9±0.4), Zn (276.1±7.4), Pb (0.86±0.08), As (6.9±0.5).
Over-weight and normal-weight subjects didn't significantly differ regarding urinary concentration of any of the determined trace elements. Over-weight boys had however lower urinary Se concentration when compared to over-weight girls (9.8±0.5 vs. 11.7±0.8; p=0.01). The same difference was determined in normal-weight population (10.9±0.4 vs. 11.6±0.3; p=0.02).
There was a statistically significant (weak) negative correlations between BMI and urinary Se, Cr and Cd concentration (r_s=-0.116 (p=0.01), r_s=-0,119 (p=0.01) and r_s=-0,097 (p=0.04), respectively). When data were analysed for boys and girls separately, only a tendency to a negative correlation remained.
Conclusions: Adolescent's Se, Cr and Cd status negatively correlated with BMI. Sex dependant differences in Se levels were determined. Trace elements status and nutritional status seem to be associated.

P2-d3-773 Fat Metabolism, Obesity 9

Overweight/obesity and serum total cholesterol trends in Slovenian 5-year old children, 2001-2009

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Background: Childhood overweight/obesity and dyslipidemia are important public health issues leading to early atherosclerotic complications.
Objective and hypotheses: To determine trends in childhood overweight/obesity and elevated total cholesterol prevalence in 5-year old Slovenian children.
Methods: A total of 12.832 5-year old children (6308 girls/ 6524 boys) were included in a longitudinal study in the years 2001, 2003-2005 and 2009. Body weight and height was measured in all, total serum cholesterol was determined in 7554 (3706 girls/ 3848 boys) in the years 2001 and 2009.
Overweight/obesity were defined based on BMI using the IOTF criteria. Serum total cholesterol concentration was determined with cholesterol oksidase/p-aminofenazon method.
Results: Despite a positive tendency, prevalence of overweight didn't significantly change in girls (15.8 % (2001), 16.7 % (2004) and 18.2 % (2009); p=0.11) or boys (12.6 % (2001), 12.6 % (2004) and 13.2 % (2009); p=0.50). The same was determined for prevalence of obesity in girls (5.4 % (2001), 4.8 % (2004), and 6.2 % (2009); p=0.10) and boys (3.9 % (2001), 4.1 % (2004) and 4.3 % (2009); p=.10). Girls were significantly more prone to be over-

weight (OR 0.71/; p< 0.001) or obese (OR=0.75, p< 0.001).
Prevalence of increased total serum cholesterol significantly decreased in the period from 2001 (22 % girls, 16.4 % boys) to 2009 (10.8 % girls, 7.9 % boys), p< 0.001 respectively. Boys were less prone to have increased total cholesterol levels (OR O.70; p< 0.001).
There was no association between BMI and total cholesterol concentration in either girls or boys (r_s=0.091).
Conclusions: Trends in the prevalence of overweight/obesity in 5-year old Slovenian children are stabilizing and there is a significant negative trend in the prevalence of increased levels of total cholesterol, similarly to recent reports in the literature. Changes in public health policies in Slovenia could be the cause of these positive trends.

P2-d3-774 Fat Metabolism, Obesity 9

Preventing childhood obesity by reducing consumption of carbonated drinks: cluster randomised controlled trial

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Background: To determine if a school based educational programme aimed at reducing consumption of carbonated drinks can prevent excessive weight gain in children.
Methods: Cluster randomised controlled trial was carried out in Six primary schools in iran 644 children aged 7-11 years.which includes 644 children aged 7-11 years.our intervention was focused educational programme on nutrition over one school year and then we measure Drink consumption and number of overweight and obese children.
Result: Consumption of carbonated drinks over three days decreased by 0.6 glasses (average glass size 250 ml) in the intervention group but increased by 0.2 glasses in the control group (mean difference 0.7, 95% confidence interval 0.1 to 1.3). At 12 months the percentage of overweight and obese children increased in the control group by 7.5%, compared with a decrease in the intervention group of 0.2% (mean difference 7.7%, 2.2% to 13.1%).
Conclusions: A targeted, school based education programme produced a modest reduction in the number of carbonated drinks consumed, which was associated with a reduction in the number of overweight and obese children.

P2-d3-775 Fat Metabolism, Obesity 9

Waist-to-height ratio as screening tool for metabolic risk factors in children and adolescents

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Background: Waist-to-Height Ratio (WHR) is a better screening tool than body mass index (BMI) in identifying metabolic syndrome (MS) in adults and it does not have to be expressed relative to sex and age standards as BMI.
Objective: To assess the association between WHR and metabolic risk factors among children and adolescents.
Methods: A population representative sample of 1-17 year old children and adolescents in our city. 1417 subjects were included: 380 secondary school 12-17 year old adolescents, 675 primary school 4-12 year old children, and 362 preschool 1-4 year old children. Physical and laboratory examination were performed including weight, height, waist circumference, blood pressure, glucose, triglycerides and HDL-cholesterol. ROC (*Receiver Operating Characteristic*) curves were plotted. The areas under each ROC curve (AUC) and 95% confidence intervals were calculated using a nonparametric approach.
Results: Cut-off value of WHR with the best sensitivity (SE) and specificity (SP) for elevated blood pressure was 0.480 (SE=78.3%, SP=65.5%; AUC 0.71 (0.66-0.76); p< 0001), for hypertriglyceridemia 0.509 (SE=61.5%, SP=71.1%; AUC 0.68 (0.62-0.74); p< 0.001), for low HDL-cholesterol 0.483 (SE=70.2%, SP=68.1%; AUC 0.68 (0.63-0.73); p< 0.001), and for three or more risk factors 0.515 (SE=82.4%, SP=72.4%; AUC 0.84 (0.77-0.91); p< 0.001). WHR is not a predictor of hyperglycemia (AUC 0.48 (0.36-0.62); p=0.82).
Conclusion: Waist-to-Height Ratio is a good screening tool for children and adolescents with risk factors for Metabolic Syndrome.

P2-d3-776 Fat Metabolism, Obesity 9

Myeloperoxidase G-463A polymorphism in obese children with metabolic syndrome

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Background: In obese patients oxidative stress plays a big role in pathogenesis of some serious diseases and it exists even in childhood. Previously, it has been shown that myeloperoxidase (MPO) plays an important role in the initiation and progression of acute and chronic inflammatory diseases. Some studies have also demonstrated that obese children have higher MPO activity than normal children. The G-463A gene polymorphism (rs2333227), a G/A substitution at SP1 transcription factor binding site in *MPO* gene, is associated with its transcription activity and the G allele and GG genotype have been reported to be associated with increased MPO expression.
Objective and hypotheses: MPO gene polymorphism may have a role in pathogenesis of oxidative stress in obese children therefore the G-463A gene polymorphism was investigated in obese children.
Methods: A total of 100 obese children (59 girls and 41 boys, at a mean age of 12.68±2.09-year-old) and 100 children as a control group (67 girls and 33 boys, at a mean age of 12.54±2.32-year-old) were enrolled to the study. The frequencies of GG, AA and GA genotypes were compared between obese and control groups and it was also compared whether there are any differences between different genotypes regarding cardiovascular risk factors.
Results: Obese group had higher body mass index z-score, HOMA-IR, total cholesterol, triglycerides, LDL cholesterol, systolic and diastolic blood pressure and lower HDL cholesterol levels than controls. In obese group, GG, GA and AA genotype frequencies were 45%, 49% and 6% respectively whereas they were 51%, 40 and 9% respectively in control group. There was no statistically difference between groups regarding genotype groups (p=0,320).
Conclusions: The distribution of GG, GA and AA genotype in obese children with metabolic syndrome and control group were not statistically different and any relation could not to be demonstrated between MPO G-463A polymorphism and cardiovascular risk factors.

P2-d1-777 Fat Metabolism, Obesity 10

The serum ferritin level is higher in Korean male adolescents with abdominal obesity: results from the Korea National Health and Nutrition Examination Surveys (KNHANES) 2010

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Background: Previous reports showed the association between serum ferritin level and metabolic syndrome (MS) in adults.
Objective and hypotheses: To investigate the relationship between serum ferritin level and abdominal obesity in Korean adolescents.
Methods: This is a cross-sectional study. Data were obtained from the 5th Korean National Health and Nutrition Examination Survey (K-NHANES) conducted during 2010 by the Korean Ministry of Health and Welfare. A total of 1,076 subjects aged 10 - 18 years participated in the 2010 survey. Among these subjects, those with missing data were excluded. The study population included 849 adolescents (male=462, woman=387). Waist circumference ≥ 90th percentile for age and sex was diagnosed as abdominal obesity.
Results: The prevalence of abdominal obesity was 7.3% (34/462) in male and 10.8% (38/387) in female. When the mean levels of serum ferritin were analyzed, we observed significant higher values in men compared with woman (meanSE, 50.52.3 vs. 30.61.3, *P*< 0.0001). In male adolescents, the level of

serum ferritin, insulin, triglyceride, systolic blood pressure, white blood cell and HOMA-IR (Homeostasis model assessment-insulin resistance values) were higher and age was lower in abdominal obesity group than control. In female adolescents, the level of, insulin, white blood cell and HOMA-IR were higher and high density lipoprotein was lower in abdominal obesity group than control. In male adolescents, serum ferritin level showed positive correlation with age (r=0.409, $P< 0.0001$), triglyceride (r=0.093, $P< 0.045$), high-density lipoprotein (r=-0.152, $P< 0.001$), systolic blood pressure (r=0.177, $P< 0.0001$), diastolic blood pressure (r=0.254, $P< 0.0001$), body mass index (r=0.224, $P< 0.0001$).

Conclusions: The present study showed that high serum ferritin level is associated with abdominal obesity and some diagnostic MS index in Korean male adolescents.

P2-d1-778 Fat Metabolism, Obesity 10

No difference in serum adiponectin, resistin, TNFR1 and TNFR2 in obese adolescents with or without insulin resistance

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Background: Abnormal adipokines in obesity may contribute to insulin resistance.

Objective and hypotheses: The aim of the study was to evaluate the correlation between adiponectin, resistin, receptors of tumor necrosis factor (TNF) and insulin resistance, lipid profile or anthropometrics in obese adolescents with or without IR.

Methods: Fifty-seven obese adolescents were enrolled. According to homeostasis model assessment (HOMA), these obese were divided into two subgroups: subjects with insulin resistance (IR, HOMA≥3.4, n=42) and without IR (HOMA< 3.4, n=15). Thirty-four adolescents with normal weight and without insulin resistance were included as control. The serum levels of adiponectina, resistin, TNFR1 and TNFR2 were measured by ELISA.

Results: The all studied obese adolescents showed higher levels in triglycerides, glucose, insulin, HOMA than control subjects. The obese also presented decreased adiponectin (5.6±2.6 μg/ml) and increased resistin (30.6±9.3 ng/ml) compared with controls (7.3±2.7 μg/ml and 23.2±8.5 ng/ml, respectively). No difference was observed in the two receptors of TNF-α between obese and control groups. No significant difference in adiponectin, resistin, TNFR1 and TNR2 was observed in the obese subgroups with or without IR. By Pearson analysis, adiponectin was associated inversely with waist circumference (WC) and systolic blood pressure, while resistin was positively with BMI and WC in all obese subjects. By multiple linear regression analysis, WC was the only significant predictor for the variance of serum adiponectin levels in obese adolescents. No significant association was observed between adipokines and HOMA in obese subjects.

Conclusions: No difference in adiponectin, resistin, two receptors of TNF-α in obese adolescent with or without IR suggested further investigation to explore the association between abnormality of adipokines and insulin resistance.

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The distinction of metabolically 'healthy' from metabolically 'unhealthy' obese children and adolescents

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Background: Most of the obese children show metabolic disturbances such as impaired glucose tolerance, insulin resistance and dyslipidemia. Healthy obesity describes the absence of any metabolic disorder including type 2 diabetes, dyslipidemia and hypertension in an obese individual (Bluher, 2010).

Objective and hypothesis: We aimed to identify and compare metabolically 'healthy' with metabolically 'unhealthy' obese children. We hypothesized that an unfavourable metabolic profile, rather than a high BMI, is associated with a higher risk for type 2 diabetes.

Methods: We retrospectively analysed data from 162 obese (mean ± SD BMI SDS: 2.7±0.6) children (91 girls) aged 10 to 18 yrs (age: 13.4±1.8 yrs) who underwent an OGTT between May 2004 and January 2012. Plasma glucose, insulin, HDL-cholesterol and triglycerides concentrations were measured. Metabolically 'healthy' obese (MHO) children were defined as having none of the components of the MetS except obesity; metabolically unhealthy obese (MUO) were defined as having at least one additional component of the MetS (Zimmet et al., 2007).

Results: 29 (18 %) of the subjects did not have any component of the MetS. There were no differences in age (MHO: 12.9±1.6 yrs; MUO: 13.4±1.8 yrs) nor BMI-SDS (2.6±0.6 vs 2.8±0.6) between both groups. Fasting glucose was comparable (88±6 mg/dl vs 90±8 mg/dl). Fasting insulin (16±9 μU/ml vs 24±13 μU/ml; p< 0.001), 2-hour glucose (107±15 vs 118±24; p=0.002), 2-hour insulin (75±63 μU/ml vs 128±114 μU/ml; p=0.005), HOMA-IR (3.5±2.3 vs 5.5±3.1; p< 0.001) and HOMA-%B (255±174 vs 346±240; p=0.006) were lower in the MHO group.

Conclusion: About 20% of the studied obese children are metabolically 'healthy'. These subjects had a better glucose tolerance, insulin sensitivity, and beta-cell function compared to metabolically 'unhealthy' ones. Early identification of metabolically 'healthy' versus 'unhealthy' obese children is recommended in order to provide better targeted and personalized therapies.

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Family history, perinatal factors and feeding behavior during the first year of life in obese children with metabolic syndrome and those with healthy metabolic phenotype

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Background: Most of what is known about the metabolically healthy obese phenomenon is derived from studies in adult population. When humans eat more and exercise less, they tend to become obese and unhealthy. However some individuals are relatively protected against cardiometabolic risk despite significant obesity, referred as the "metabolically healthy obese group".

Objective: The aim of this study was to determine if family history, perinatal factors and feeding habits during the first year of life are associated with favorable metabolic profile in the obese pediatric patients.

Methods: Case-control study setting in a Pediatric Obesity Clinic at Hospital General de Méxicol. Cases of obese children with metabolic syndrome were classified when abdominal obesity was present and two or more of the following (elevated triglycerides, low HDL-cholesterol, high blood pressure, increased plasma glucose). One control for each case with normal parameters of blood pressure, glucose and lipid profile (metabolically healthy controls) were matched for age, sex and BMI.

Results: We included 32 cases (17 girls and 15 boys, mean age 12.2 years SD ± 3.8 years, mean BMI 27.7 SD ± 4.5 kg/m$^{2)}$, and 32 matched controls (mean age 12.2 years SD ± 3.5, mean BMI 27.6 kg /m^2 SD ± 3.77). A history of threatened abortion was associated with an increased risk of metabolic syndrome (OR 1.67, 95% CI 1.4-2.6), as well as breastfeeding for less than 6 months (OR 2.12, 95% CI 1.12-4.01). No differences were observed regarding family history of cardiovascular and metabolic diseases in two previous generations nor other perinatal factors.

Conclusions: Perinatal factors such as a history of threatened abortion and breastfeeding for less than six months are associated with an increased risk of metabolic syndrome in pediatric obese patients regardless of age, sex and BMI.

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Sitosterolemia in a 2-year-old girl with dermal and hematological expression

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Introduction: A case of a 2-year-old girl with fitosterolemia with tuberous xanthomas and erythrocytes abnormalities is presented. According to the literature, this case would be the first in a child with this entity in our country as well as the first described in Maghreb ethnic.
Case study: A girl presenting tuberous xanthomas associating strikingly elevated serum cholesterol levels. Pregnancy and birth normal, young consanguineous parents (first cousins) of Maghreb ethnicity. No family history of lipid profile alterations or premature heart disease.
Physical examination was normal except the presence of tuberoses xanthomas located over her elbows, wrist, knee and ankle. Pathology of the dermal lesions showed, foamy histiocytes with abundant lipid content.
Serum lipids: 623 mg/dl TC, 570 mg/dl LDL-c, 319 mg/dl B Apolipoprotein. Gas chromatography analysis showed Sitosterol 927 µmol/L (< 3.0) and Campesterol 387 µmol/L (< 3.0) representing an increase until 300 percent above normal values. Presence of erythrocyte anisocytosis and numerous large platelets were found. General biochemistry and endocrinological study, hemoglobin electrophoretic as well as of the genotype of the alpha chains study were normal.
Ultrasound trunk carotid and cardiac study was normal.
Genetic study: Mutation in homozygosis (p.Gly574Arg) in the gene ABCG8. The parents are carriers of the same mutation in heterozygosity.
We have started treatment at the age of 3 years with Ezetimibe 5 mg/day presenting 2 months later a decrease 57% in levels of sitosterol (954-403 µmol/L) and 22% in the Campesterol (376 to 293 µmol/L). Not side effect to medication.
Spontaneous regression of cutaneous xanthomas and normalization of cholesterol before ezetimibe treatment was noted.
Conclusions: We present a rare disease of lipid metabolism (70 cases worldwide) in a little girl with dermal and hematological expression.

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ACE inhibitors have positive effects on insulin resistance and lipid profile in children with metabolic syndrome

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Background: Angiotensin-convertingenzyme (ACE) inhibitors prevent ACE enzyme, which in turn blocks the production of angiotensin II from angiotensin I. We evaluated the effects of ACE inhibitors on insulin resistance, glucose metabolism, liver fattening, and lipid profile in male and female children over 10 years of age with obesity-associated metabolic syndrome.
Methods: A total of 53 children with metabolic syndromeenrolled in the study. Thirty obese children who were not using an ACE inhibitor (13 female, 17 male), and 23 who were using an ACE inhibitor (13 female, 10 male) were divided into two groups. Results were evaluated with a 95% confidence interval, and a significance level of 0.05 ($p < 0.05$).
Results: Anthropometric and laboratory data comparison of the groups at 3rd, 6th, and 12th months revealed no statistically significant differences in terms of weight SDS, BMI SDS, weight for height percentile, body fat percentage, and VLDL values. However, there were statistically significant differences in mean glucose and insulin levels, HOMA-IR, LDL and HDL values, and highly significant differences in mean triglyceride values. There was also a statistically significant difference between the groups in terms of hepatosteatosis grades, in favor of the group using ACE inhibitors.
Conclusions: The positive effects of these drugs, particularly on the most important criteria of metabolic syndrome, hypertriglyceridemia and insulin resistance, might bring them forth as the first choice of drugs in the treatment of obese and hypertensive children. Randomized, controlled, double-blind, and long-term studies are needed for a definitive conclusion. ACE inhibitors have positive effects on insulin resistance and lipid profile in children with metabolic syndrome.

P2-d1-783 Fat Metabolism, Obesity 10

Experiences implementing obesity services for children and adolescents (OSCA) consensus guidelines in a secondary care setting for children with obesity

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Background: In 2012, the Obesity Services for Children and Adolescents (OSCA) Group produced consensus guidelines on the investigation of children with obesity in the secondary care setting
Objective and hypotheses: We conducted a prospective audit in a Paediatric Endocrinology Outpatient Clinic to determine the impact of applying these guidelines. 26 patients with BMI > 98th centile were randomly selected. Mean age at presentation was 8.3 years (± 3.5 years). 13 of these patients had a BMI > 3.5 SD above the mean. The remaining patients had been referred for investigation of aetiology or complications.
Results: With the exception of 2 infants, all children had blood pressure recorded at presentation. The majority of children received baseline investigations including oral glucose tolerance (12), liver function tests (17), and lipid profile (13). 8 children had thyroid function tests, 21 children additional endocrine tests and 5 children were enrolled in the Genetics of Obesity study. 5 children were referred for sleep studies. 4 children had complications on presentation including insulin resistance requiring metformin, non-alcoholic steatohepatitis, depression and slipped upper femoral epiphysis. 2 children had underlying hypothyroidism.
All children were offered referral to a weight management programme, with 75% uptake and 50% completion rate. 19 children were offered dietician follow up, the attendance rates for which were poor. The average fall in BMI over a 10 week weight management programme was from 35.5 to 31.5. For the complete cohort, however, there was an overall gain in BMI over a 2.5 year follow up period from 28.8±4.9 to 31.6±6.0.
Conclusions: Our findings suggest that referrals to secondary care have appropriately identified children at risk of obesity related morbidity. However, a significant improvement in weight loss is only likely in a multi-disciplinary set up sustained over time.

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To study the HDL-cholesterol metabolism in the offspring of patients with type 2 diabetes mellitus

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Background: Patients with Diabetes mellitus develop low levels of HDL during the initial progression of disease. There is the growing appreciation that insulin resistance is associated with the lowering of HDL-C,although the exact prevalence of the insulin resistance syndrome among those with low HDL-C in the general population has not yet been clearly established.
Objective and hypotheses: The present study was aimed to find the relationship of insulin resistance with sub components of HDL.
Methods: One thirty one patients and fifteen controls were taken.The study was approved by the institute ethics comittee as per ICMR guidelines. 5 ml serum was taken and assayed.A precipitation reagent (0.06 ml) containing 1,071 U/ml heparin, 500 mmol/l MnCl2, and 12 mg/ml dextran sulfate was added to a serum (0.3 ml). The sample was incubated and centrifuged at 10,000 rpm for 10 min. HDL3-C was measured by a homogenous HDL-C assay in the supernatant, and HDL2-C was estimated by subtracting the HDL3-C from the direct HDL-C.

Results: Mean HDL of patients and controls was 37.52 ± 12.15 and 31.13 ± 9.841 respectively. HDL2 comparision between patients and controls resulted 20.04± 6.73 and 18.22 ± 5.38 respectively. HDL3 comparision between patients and controls resulted 17.40 ± 11.35 and 12.91 ± 6.07 respectively. LDL comparision between patients and controls resulted 97.63 ± 32.94 and 101.67 ± 32.50 respectively.
TG comparision between patients and controls resulted 126.15 ± 67.14 and 148.00 ± 111.72 respectively. VLDL comparision between patients and controls resulted 26.81 ± 17.79 and 34.12 ± 26.43 respectively. Insulin comparision between patients and controls resulted 9.86 ± 8.20 and 9.67 ± 3.7 respectively.
Conclusions: This study resulted that HDL2 is higher than HDL3 in offsprings of patients with type 2 diabetes mellitus as compare to controls. This is further indication to become diabetic.Further analyses will be done till more sample size is collected.

P2-d1-785 Fat Metabolism, Obesity 10

Clinical and analytical characteristics of children with severe hypercholesterolaemia. Genetic and ultrasound carotid intima-media thickness studies

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Objective: To describe clinical and laboratory characteristics of patients with severe hypercholesterolemia in the last 10 years. Genetic study. Assess impacts in arteries by ultrasound carotid intima-media thickness (cIMT) measurement.
Population and methods: Retrospective study of patients diagnosed with severe hypercholesterolemia. Genetic study of LDL receptor (LDLR) gene in blood, B-mode ultrasound examination of cIMT in the rear wall of the common carotid artery with linear 12MHz transducer.
Results: N=32: 50% male and 50% female, 71.9% consulted for hypercholesterolemia. Three adopted patients (9.4%): 2 mutation, 1 total deletion. The rest with family history of severe hypercholesterolemia. The 50% had comorbidity (obesity (28.1% BMI>2SDS), hypothyroidism, short stature, pseudohypoparathyroidism, type 1 diabetes). Mean age at diagnosis 7.2 ±3.1 years. Maximum Total cholesterol 282.2 ±38.9 mg/dl, LDL-C of 207.6 ±42.6mg/dl, HDL-C 65.2 ±20.4 mg/dl. Apo-A 143.3 ±40.5mg/dl, Apo-B 119.6 ±27.8mg/dl, lipoprotein (a) 31.2 ±26.9mg/dl. LDLR genetic study of 20 children, findings: 12 mutations, 4 deletions, 4 without genetic alteration in present study. cIMT study in 23 (11 males and 12 female), mean 0.53 ±0.1mm(0.35-0.80). The cIMT is increased compared with published data from healthy children. In spite of the fact that total cholesterol and LDL-C decreased significantly (p< 0.001) with dietary treatment and phytosterols, nowadays 7 patients (6 with positive genetic study) already are with pharmacological treatment.
Conclusions: Genetically based hypercholesterolemia is serious and requires early intervention. The genetic confirmation strengthens the diagnosis of disease severity. cIMT studies alert of the cardiovascular risk from childhood. Drug therapy is more effective than isolated dietary treatment.

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Vitamin D supplementation in an urban paediatric weight management program

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Background: Obesity is a risk factor for vitamin D (vitD) deficiency. Some professional societies recommend screening for this problem in obese children. The effectiveness of screening and treatment in pediatric weight management programs is unclear.
Objective and hypotheses: This study aimed to describe (1) the treatment of vitD deficiency and (2) patient adherence to treatment in an urban pediatric weight management program performing screening.
Methods: This was a retrospective review of new patients seen from 9/1/2008 to 12/31/2010. Data were collected from visits prior to 7/1/2011.
Results: 794 charts were reviewed. 594 patients had a serum 25-hydroxyvitamin D [25(OH)D] drawn within 6 months of the initial visit (mean 23.3±8.8 ng/mL). VitD supplementation was reported by 2.8% of patients at the initial visit and was recommended by providers at 50.6% of all initial visits and 73.4% (157/214) of initial visits for patients with 25(OH)D< 20 ng/mL. Patients receiving recommendations for vitD had lower 25(OH)D (20.8 vs. 27.5 ng/mL, p< 0.001). Cholecalciferol 2000 IU daily was the most common regimen recommended (44.8%), followed by 1000 IU daily (38.1%). Most patients received recommendations at the visit (66.0%), but length of therapy and maintenance recommendations were variable. Among those presenting for follow-up (N=407), 93 patients (22.9%) reported current intake of vitD at the first follow-up visit, and most (89.2%) after a documented provider recommendation at the initial visit. Of patients not taking vitD at the follow-up visit, 132 (42.0%) received recommendations for vitD at the initial visit.
Conclusions: Despite institution of screening for vitD deficiency in this program, recommendations for supplementation were variable. Further, the challenges of attrition from pediatric weight management programs and patient nonadherence raise questions as to whether treatment for vitD deficiency may be more successful when overseen in primary care.

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Association between non-alcoholic fatty liver disease and mean platelet volume in obese children and adolescents

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Background: The increase in non alcoholic fatty liver disease (NAFLD) is relevant to grow of childhood obesity which has grown in the past decades. NAFLD is interrelated with cardiovascular disease.
Platelet activation and aggregation are important in the coronary heart disease. Mean platelet volume (MPV) defines the platelet activation.
Objective and hypotheses: The aim of this study is to investigate the relationship between NAFLD and MPV in obese children and adolescents.
Methods: A total of 135 children (58 boys and 77 girls between the ages of 10-18) admitted to endocrine outpatient clinic because of obesity were enrolled.
Fasting blood glucose (FBG), insulin, total cholesterol (T. cholest.), high density lipoprotein (HDL), triglyceride (TG), liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT)) were analyzed. Patients were divided into two groups according to the absence or presence of NAFLD.
Result: The prevalence of NAFLD was 29.6%. MPV was significantly higher in obese patient with NAFLD than without NAFLD. Liver functions tests, insulin, t.cholest. and triglyceride were significantly higher in the NAFLD group. There was a positive correlation between GTT, FBG and MPV. In logarithmic analysis, NAFLD was found significantly pozitivw associated with lower MPV (Odds Ratio (OR) 0.62, p: 0.030).
Conclusions: It has been proven with this study that patients with NAFLD have higher MPV.
MPV can be used as a possible indicator and follow-up marker of NAFLD in obese children and adolescents.

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Vitamin D levels in obese compared to normal weight children

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Background: Adequate levels of Vitamin D are essential for bone health in growing children. These depend on balanced nutrition and moderate sunlight exposure.
Objective and hypotheses: Compare vitamin D levels between obese and normal weight children.
Methods: We studied 180 obese children (105 girls and 75 boys) (group 1) with age of 8.5 ± 1.2 years and body mass index (BMI) ≥ percentile 95 for

age and sex. 175 normal weight children (98 girls, 77 boys) (group 2), were included, age 9.1 ± 0.8 (M ± SD) years with BMI normal for age and sex. Vitamin D levels were measured in morning plasma sample in both groups. Milk consumption and open-air activities were also recorded in both groups. Normal level of Vitamin D was taken as ≥ 20 ng/ml.

Results: In group 1, 42 % (40 girls, 35 boys) had Vitamin D levels in 15 ± 2.5 ng/ml (< 20 ng/ml), the other 58 % had levels of 32 ± 4.5 ng/ ml. diary consumption was 300 ± 50 ml/ day and only 25 % practiced open air activities for 15 ± 5 minutes daily.

In group 2, 20 % (20 girls, 15 boys) had Vitamin D levels 18.3 ± 3.2 ng/ml (< 20 ng/ml), the other 140 had levels of 38 ± 5.5 ng/ ml. diary consumption was 350 ± 100 ml/ day, and 55 % practiced open air activities for 30 ± 15 minutes daily. No significant sex differences were observed.

	% Deficiency	Deficient level	Normal level	Milk consumption	open air activities
obese	42 %	15 ng/ml	32 ng/ml	300 ml / day	15 minutes
normal	20 %	18 ng/ml	38 ng/ml	350 ml / day	30 minutes

[table 1]

Conclusions: Obese children are in a higher risk of Vitamin D deficiency than normal weight. Diary consumption and open-air activities provide simple protective measures to ensure adequate supplies of vitamin D and adequate future bone formation.

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Body image of normal, overweight and obese adolescent girls

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Introduction: In each community, the social and cultural background influences the perception of body image and ideal size. However, the media convey a body ideal that is thinner than ever at a time when our young people are heavier than ever.

Objective: The objective of this study was to estimate the prevalence of overweight and obesity, to figure out how normal, overweight and obese adolescents think of themselves and how many of them intend to go on a slimming diet or already are on a diet.

Method: During a multistage stratified cluster sampling, 20 secondary schools (6th to 11th grades) were selected from different zones in Tehran and 1700 females aged 11-17 years were assessed.

Results: The overall mean prevalence of overweight and obesity were 14.7 and 6.45 in girls.

24% of normal students considered themselves as fat, 52% as balanced and 24% as thin. For the overweight students, 78.9% considered themselves as fat, 19.1% as balanced and 2% as thin! And finally for the obese students, 89% considered themselves as fat, 10.1% as balanced, and 0.9% as thin (P< 0.05). 94.5% of obese students were planning to go on a diet. This number fell to 85.8% for overweight students. Surprisingly 42.5% of normal students were planning to diet as well.

Conclusion: In this study, acceptance of body size was somehow realistic among overweight and obese adolescents, while one third of normal students considered themselves as "fat". Similar to the researches done before, in our study, girls demonstrated an exaggerated preoccupation with body image. Not only the overweight and obese girls, but also normal girls considered themselves too fat and reported that they were currently trying to lose weight. This emphasizes the importance of self image in adolescents and its effect on social behaviors.

This epidemic trend to go on a diet can harmfully affect the adolescents' intake of macro- and micronutrients.

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Relationship of FABP4 and adiponectin levels in adolescents with obesity

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Background: Obesity in children is associated with a future risk of developing metabolic disorders in adults. Studies in adults have shown that high serum fatty acid-binding protein 4 (FABP4) levels and low serum adiponectin levels are associated with an increased risk of type 2 diabetes and cardiovascular disease. The relationship of these levels in children has not yet been examined.

Objective and hypotheses: To measure FABP4 serum levels in obese and normal weight adolescents and to evaluate its relationship with adiponectin levels.

Methods: The study included 65 obese adolescents (SDS BMI 3.1±0.5, age 15.6±1.4 years, 43 boys, 22 girls) and 14 normal weight adolescents (SDS BMI -0.06±0.6, age 15.3±1.1 years, 7 boys, 7 girls). The groups were matched by age, sex and Tanner stages. FABP4, adiponectin, anthropometric and metabolic parameters were measured.

Results: Serum FABP4 levels were significantly higher in the obese group compared to the normal weight group (19.8±8.4 vs 8.1±2.4 ng/ml, p< 0.001). The adolescents with obesity compared to the normal weight group also had significantly lower levels of adiponectin (12.9±5.2 vs 18.6±5.8 μg/ml, p< 0.001), especially in patients with insulin resistance. In the obese adolescents the serum FABP4 level negatively correlated with serum levels of adiponectin, independent of SDS BMI (β = -0.34; p=0.002).

Conclusions: Adolescents with obesity have a higher serum concentration of FABP4 than normal weight adolescents. This elevated FABP4 level does not depend on the degree of obesity and negatively correlated with serum levels of adiponectin. The present results suggest that the decrease in adiponectin levels and the increase in FABP4 can be used as an additional biomarker to identify high-risk groups for the development of metabolic complications, related to obesity.

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The role of leptin and ghrelin in obesity development after adenoidectomy or adenotonsillectomy

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Background: Accelerated weight gain after (adeno) tonsillectomy has been reported in a number of studies. Whether (adeno) tonsillectomy is also a risk factor for development of overweight is unknown.

Objective and hypotheses: We investigated whether leptin and ghrelin have any effects in development of obesity after (adeno)tonsillectomy.

Methods: We studied 31 patients and 29 age- and sex-matched healthy control children. All subjects underwent auxologic evaluation, biochemical investigations before surgery and 1-year after.

Results: One year after, height-SDS (P=0.001) and weight-SDS (P=0.004) were significantly increased in both groups. No changes in BMI-SDS (P=0.105) were observed. Preoperative leptin levels were significantly higher in patients than controls (P< 0.001). IGF-1, IGFBP-3, HOMA-IR and ghrelin levels were not significantly different between the groups. After one year, IGF-1 (P=0.001) and IGFBP-3 (P=0.001) were significantly increased, while ghrelin was significantly decreased (P<0.001). Leptin levels of patients were also significantly higher than preoperative values (P=0.036).

Conclusions: Significantly higher leptin levels in patients compared to control both before and one year after an obstruction-relieving surgery suggested that higher levels might be due to leptin resistance in these patients. Based on our findings we recommend measurement of leptin levels longitudinally for at least 5 years after adenotonsillectomy.

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Six-month outcomes of family-based multidisciplinary treatment of childhood obesity

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Background: Obesity is a widespread child problem, which increases the risk of adult obesity, morbidity and mortality.
Objective: To determine whether a multidisciplinary family-based behavioral lifestyle intervention effectively improves Body Mass Index Percentiles (BMI-P) in overweight (85%≤BMI-P< 95%) and obese children (BMP-P≥95%).
Methods: A total of 307 overweight and obese children (mean BMI-P 97.05+/-2.54%), aged 6-13 years (mean 9.4 ± 1.6), participated in an intensive 6 months family-based multidisciplinary cognitive behavioral intervention that treats pediatric obesity using medical management, nutrition education, behavioral intervention, and physical activity. Child BMI-P measured at baseline, after 3 months, and at the end of the intervention.
Results: 257 children (84%) completed the program in full. The intervention was associated with a significant decrease in BMI-P after 3 and 6 months: -1.58±1.10% and -3.67+/-2.71%, respectively ($p < 0.0001$ vs baseline). 34.9% of overweight children achieved normal weight (BMI-P < 85%) and 22.9% of obese children achieved BMI-P at the overweight category range. Baseline BMI-P was found to be a significant predictor of treatment success. A decrease in 1 unit resulted in a 1.6 fold (95% confidence interval 1.4-1.9) increase odds of success.
Conclusions: A family-based behavioral lifestyle multidisciplinary pediatric weight management program can improve the weight status of obese and overweight children. Higher pre-intervention BMI percentiles were associated with less favorable responses to the intervention.

P2-d2-793 Fat Metabolism, Obesity 11

The role of hereditary risk factors in children and adolescents with overweight and obesity

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Background: About a 60% of adults with obesity had gained weight already in childhood. Investigation of family anamnesis can help to predict the risk factors and progression of overweight (OW) and obesity (O) in a child.
Objective: The aim of the study was to analyze hereditary risk factors for development of OW and O in children.
Methods: *Target group*: children and adolescents 10-18 y.o.: Group 1 (Gr1) - 45 OW children, Group 2 (Gr2) - 55 O children, control group (CGr) - 35 healthy children with normal BMI.
Diagnostic criteria: Body mass index (BMI) over the 85-th percentile for age and sex (CDC, 2000) for OW children, BMI over 95-th percentile for age and sex for O children.
Family anamnesis of obesity, Diabeses Mellitus Type 2 (DM T2), arterial hypertension (ArtH) was investigated (in parents and in grandparents).
Results: The patients in both groups had positive family anamnesis for obesity, DM T2 and arterial hypertension. Relatives from Gr1 had obesity in 1/2 of cases (mainly in mothers). In Gr2 ¾ of the children had relatives with obesity, in this group it was seen equally oft in fathers (38.18%) and in mothers (41.81%), as well as more often in grandparents compared to Gr1 Frequency of DM T2 in relatives was higher in Gr2 (30.91%) compared to Gr1 (15.69%) and CGr (11.43%). In all groups most frequent was the anamnesis from mother's site positive, but most common in Gr2 (21,82%). Positive anamnesis for ArtH was in half of the patients in Gr1 and 2, and only in 22,86% in CGr. In Gr2 ArtH was often seen not only in relatives from mother's site like in Gr1, but in all relatives.
Conclusions: Children with OW and O very oft have positive family anamnesis for obesity as well as for two main complications of obesity (DM T2, ArtH). OW and O are hereditary. The more family members have mentioned diseases the higher is the risk of developing the pathological weight gain and it's progression in childhood, especially when a mothers of a patient has positive anamnesis.

P2-d2-794 Fat Metabolism, Obesity 11

C-reactive protein and food consumption: interrelationship with features and frequency of metabolic syndrome in obese and non obese children and adolescents

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Background: This study aimed to analyze the frequency and its characteristics of the metabolic syndrome (MS) in obese and non-obese children and adolescents, correlating them with the C-reactive protein (CRP), food intake and insulin resistance.
Method: Two groups were selected, matched by age and sex: one of 65 children and adolescents between eight and fifteen years old, obese, and the other with 30 non-obese. Anthropometrics and biochemical measurements were also realized. The high-sensitive test to analyze the CRP and the determination of the insulin resistance, calculated by Homeostasis Model Assessment (HOMA-IR). Among the various proposals to the definition of the metabolic syndrome, was selected the one adapted by Cook et al. A questionnaire of frequency of food consumption was applied and processed the data by the Dietsys Program. The results were analyzed with the R software.
Results and discussion: The frequency of the metabolic syndrome was 49% in obese and 6% in non-obese, no significant difference between sex, age or pubertal staging and the SM. In the obese group, the CRP, abdominal circumference, systemic blood pressure, BMI and the stacks of triglycerides, were significantly higher. Yet there were differences between LDL, fasting glucose, HOMA-IR and low levels of HDL. Comparing the mean food consumption among these groups, there was significant difference among the assessed variables. When applying the linear regression model was found a linear relationship between CRP (independent variable) and BMI (dependent variable). The same was not verified by HOMA-IR index, or with other components of MS.
Conclusion: Metabolic syndrome seems to have obesity as epiphenomena, from which its other components are associated. The insulin resistance index measured by HOMA-IR is not the parameter of metabolic syndrome in children and adolescents. CRP levels correlate directly with obesity, using BMI, which may be cast on criteria in the diagnosis of MS in this population.

P2-d2-795 Fat Metabolism, Obesity 11

Determinants and correlates of vitamin D deficiency in obese adolescents

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Background: Obesity and adolescence are risk factors for vitamin D deficiency and are associated with a higher risk for metabolic changes such as insulin resistance and increased inflammation.
Objective and hypotheses: To investigate the prevalence of vitamin D deficiency and its relationship with cardiovascular risk factors (serum parameters of metabolic syndrome and chronic inflammation) in a group of obese young adolescents.
Methods: Body composition by DXA, fasting serum markers for metabolic syndrome, insulin resistance and chronic inflammation, and 25-OH vitamin D (by immunoassay) were studied in 95
(36 boys) obese adolescents entering a residential weight loss program in July 2012. Their median (range) age was 14.7 years (10.6 - 19) and BMI z-score was 2.7 SD (1.8 - 4).
Results: Mean 25-OH vitamin D level was 18.6 µg/L (range 3.8-41.8) and 57 (60%) had a level
< 20 µg/L. No sex difference in 25-OH vitamin D levels was present, while subjects from non-European ethnicity (n=27) had significant lower levels ($p < 0.001$). 25-OH vitamin D correlated significantly with body fat mass ($r = -0.24$, $p=0.02$), BMI z-score ($r = -0.29$; $p=0.004$) and waist z -score ($r = -0.27$; $p=0.009$), but not with age, pubertal stage, and the studied parameters of inflammation (hsCRP, fibrinogen, uric acid), insulin resistance (SHBG, insulin, Quicki, HOMA), or the metabolic syndrome (glucose, HDL cholesterol, triglycerides).
Conclusions: A low vitamin D reserve was found in 60 % of obese children

during summertime. A more severe adiposity and a tanned skin color were risk factors for hypovitaminosis. No relationship between circulating 25-OH vitamin D and the parameters of metabolic syndrome were seen in the studied group of obese adolescents entering a residential weight loss program.

P2-d2-796 Fat Metabolism, Obesity 11

The relationship between serum 25-hydroxyvitamin D and inflammatory cytokines in obese children

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Background: The morbidity of obesity in children around the world is increasing and become a great concern of public health.
Objective and hypotheses: Obesity and the following insulin resistance are thought to be caused by the chronic inflammatory, which may be induced by the changes of cytokines. It has been a little more than 20 years to know that vitamin D can exert effects on cells of the immune system. To study the association between serum 25-(OH)D concentration and inflammatory cytokines in obese children.
Methods: The children had their routine physical examination in our clinics from February to June 2012 were divided into 2 groups (Obese group and Control group) according to body mass index (BMI). Obesity was defined as BMI≥P95. Serum 25-(OH)D, interleukin(IL-6,IL-8), interferon-γ（IFN-γ）and anti-tumor necrosis factor-α(TNF-α) were measured.
Results: The level of 25-(OH)D was significantly lower in obese group than that in the control group. According to the level of serum 25-(OH)D, patients were divided into normal, insufficient and deficient groups. There were no significant differences as to the level of proinflammatory cytokines among the groups. However, the association of 25-(OH)D concentration with IFN-γ was observed in the obese group (p = 0.04).
Conclusions: Obese children had lower 25-(OH)D level compared with children in control group. 25-(OH)D concentration was found to be related with BMI (r=-0.533,p=0.00) but not with inflammatory cytokines.

P2-d2-797 Fat Metabolism, Obesity 11

Unique treatment and rapid resolution of extreme hyperlipidemia in a 7-year-old female with new onset diabetes, treated with L-carnitine and continuous insulin infusion

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Introduction: Although, rare cases of extreme hyperlipidemia with pancreatitis in acutely sick children with new onset diabetes have been reported, our patient had the highest reported triglycerides (TG) in a child with new onset diabetes without pancreatitis. Previously reported pediatric treatment included use of plasmophoresis and 4 weeks of insulin drip.
Case study: We report a 7 year old girl who presented with polyuria, polydipsia. Her initial serum glucose was 795 mg/dl. Patient was not in DKA and was started on SQ insulin. Her initial blood had lipemic apperance and showed TG of 17,927 mg/dl and total cholesterol of 914 mg/dl. She was started on IV insulin drip, IV fluids and made NPO.
L-Carnitine has been used to reduce extreme hyperlipedimia in infants with congenital CPT1 deficiency and also have been used in treatment of hyperlipidemia in adults with type 2 diabetes. Carnitine profile was obtained and pt was started on Levocarnitine (50 mg/kg/daily). Patient continued on IV insulin drip, NPO and was started on TPN. In 5 days her TG decreased to 294 mg/dl. Patient was started on PO feeds and sq insulin. Her TG increased again in 24 hours to 706 mg/dl. At that time the pt was switched from sq Lantus/Novolog to Novolog CSI via insulin pump. In 2 days, her TG further decreased to 421mg/dl and she was discharged home on oral levocarnitine, Novolog via insulin pump, Lipitor and low fat diet.
Results: In 6 weeks the lipid profile normalized with TG of 62 mg/dl and LDL of 122 mg/dl. The carnitine profile showed mild carnitine defficiency. Lipid electrophoresis showed that she may have familial hyperlipedimia type IIa. A year later pt is doing well on insulin pump therapy and oral carnitine.
Conclusions: L-carnitine and CSI insulin therapy may play important role in fast normalization of lipid profile in children with extreme hyperlipidemia and diabetes. L-carnitine should be further investigated in treatment of children with diabetes and hyperlipidemia.

P2-d2-798 Fat Metabolism, Obesity 11

Are body mass index and family history of cardiovascular disease predictors of abnormal lipid profiles in children and adolescents?

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Background: Dyslipidaemia is an established risk factor for cardiovascular disease (CVD) among adults. The American Academy of Paediatrics(AAP) recommends screening children and adolescents with a fasting lipid profile, and focuses on improving childhood and adolescent lipid and lipoprotein concentrations to lower the lifetime risk of CVD.
Objective and hypothesis: The aim of this study was to compare lipid profiles of children and adolescents with either normal or increased body mass index(BMI) in relation to their family history (FH) of CVD.
Methods: Height, Weight, BMI, plasma total cholesterol, low-density cholesterol(LDL), high-density cholesterol (HDL), triglycerides(Tg), and family history(FH) for CVD were obtained for 45 normal weight children (16 boys, 29 girls)-group 1, and 50 overweight/obese children (22 boys, 28 girls)- group 2.
Results: Childrens' mean decimal age was 10.1(range 3.72-17.51) and 10.69 (2-25-13.54) years old respectively. BMI was normal for age for group1, ≥85th percentile for group 2. Lipid profiles for borderline(170-199mg/dl) and increased total cholesterol(>200mg/dl) and borderline LDL((110-129mg/dl) were similar (26% for both groups;15.7%-group 1, 8%-group 2). CVD FH was also seen in the majority of both groups (73.3% and 62% respectively). Group 2 had in 32% Tg>110mg/dl whereas group 1 had 6.6%. No statistical significance was found between the 2 groups regarding increased BMI and CVD FH(p=0.07).
Conclusions: Children with progressive atherosclerosis are most at risk of CVD in adulthood. Studies have shown that using the criterion of FH and/or BMI(≥85th percentile) improves the sensitivity of dyslipidaemia screening in childhood and adolescence. Interestingly, our results showed similar results regarding borderline total cholesterol, LDL and HDL < 40mg/dl. This finding has definitely implications in CVD prevention programmes including dietary changes and increasing physical activity to improve the later.

P2-d2-799 Fat Metabolism, Obesity 11

Long-term efficacy (12 months) after a treatment program for treating obesity

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Introduction: Previous studies have shown that one of the best pediatric therapeutic strategies in the field of overweight goes through group therapy. The clinical challenge of maintaining the long-term (> 1 year), as this would be the settlement of lifestyle changes raised.
Objective: To evaluate the effectiveness of long-term (12 months) of a comprehensive educational program and group, with parental involvement, in terms of variables associated with metabolic risk.
Methods: We recruited 40 patients (25 girls and 15 boys) between 8 and 13 years are overweight or obese. They and their parents were included in a re-education program behavior, the method "nin @ s in motion" Vall Hebron Hospital. Before starting the program, to completion and 12 months later, they determined the weight, height, the waist and hip circumferences and body composition by bioelectrical impedance multichannel. Data were analyzed

with the test for paired samples (Student t), with a confidence interval of 95%.
Results: After the completion of the program, and with only a departure, 87% of patients had reduced their BMI. At 12 months of this, it remains a significant reduction in BMI from baseline BMI program referred to P50 for age and sex (mean reduction of 10%, more significant in males). Likewise, the percentage of cases that go to normal weight after 12 months increased to more than double over the end of the program, especially at the expense of the overweight group. It also significantly reduces the% of waist circumference compared to normal population, maintaining and even improving the group of girls at 12 months after the end.

P2-d2-800 Fat Metabolism, Obesity 11

Serum adipokines profile and metabolic syndrome in obese children and adolescents

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Background: There is growing evidence that the adipose tissue is an endocrine organ, its various cellular components secreting several adipokines with important roles in obesity and its complications.
Objective and hypotheses:To characterize serum profile of adiponectin, leptin, resistin, A-FABP and lipocalin-2 in obese children and adolescents in correlation to the classic metabolic complications of obesity.
Methods: A case control study comparing 102 obese children and adolescents (age 10-18 years) cu 43 healthy normal weight controls. We measured the classical clinical and biochemical parameters of the metabolic syndrome in both groups and also the serum concentrations of adiponectin, leptin, resistin, A-FABP and lipocalin-2.
Results: Adiponectin was significantly lower, while leptin, resistin, A-FABP and lipocalin-2 were significantly higher in the obese group. There was a significant correlation between serum concentrations of the studied adipokines and the BMI Z score, negative for adiponectin, positive for all the others. A-FABP was best correlated to the systolic blood pressure adjusted for age and sex, leptin was the only adipokine positively correlated to insulinemia and HOMA-index. Adiponectin, leptin, resistin and A-FABP had a significant correlation to a proatherogenic lipid serum profile. Adiponectin was significantly lower in the obese subgroup with metabolic syndrome (MS) compared to obese children without MS, a value below 5.3µg/ml indicating with 73.8% sensibility and 61.1% specificity the MS coexistence.
Conclusions: Adiponectin first, then leptin and A-FABP are reliable biomarkers of the metabolic complications of obesity in children; lipocalin-2 was not associated to any of the classical clinical or biochemical metabolic complications.

P2-d3-801 Fat Metabolism, Obesity 12

Clinical, behavioral and family characteristics as predictors to response to therapeutic lifestyle change among overweight and obese children

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Background: The prevalence of childhood obesity is rising throughout the world, reaching epidemic proportions. Severity of obesity in children, age, gender, psychological, behavioral and other factors are possibly related to success in childhood obesity treatment.
Objective: To determine baseline predictors of treatment success in terms of Body Mass Index-Percentiles (BMI-P) in a multidisciplinary family-based behavioral lifestyle intervention for overweight and obese children.
Methods: Overweight and obese children (N= 257; age 6 - 13 years) and their caregivers participated in a prospective study and attended a lifestyle intervention. Baseline data assessment included anthropometrics, demographics, family characteristics and lifestyle. BMI-P with a target reduction of 1% or greater was measured. Logistic regressions were used for analysis.
Results: 79% of children achieved reductions in BMI-P with 50% achieving the target reduction over the course of 6 months. Baseline BMI-P was found to be the most important predictor of treatment success. Children with the lower baseline BMI-P achieving larger reductions in BMI-P over 6 months. Furthermore, Children who committed exercising regularly before the intervention, older children, firstborn children and children with non-overweight mothers were more likely to achieve greater reductions in BMI-P. No effects on treatment success were found for the number or weight status of siblings, overweight fathers or having divorced parents.
Conclusions: These results suggest that screening for baseline characteristics in childhood obesity treatment could identify who will benefit most from a pediatric lifestyle intervention. Tailored programs should be developed and the treatment team should focus on children who are less successful in achieving weight reductions. Future research should study baseline predictors of long term treatment success.

P2-d3-802 Fat Metabolism, Obesity 12

The number of smoked cigarettes per day influence adverse blood pressure and lipid levels in adolescents with obesity

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Background: The problem of smoking children and adolescents with obesity that sustains chronic inflammation in the body thereby increasing cardiovascular disease risk in adulthood is becoming progressively topical worldwide.
Objective: To compare anthropometric data, blood pressure and biochemical blood analyses in smoking and non-smoking adolescents with obesity and to evaluate the correlation with the number of smoked cigarettes per day.
Methods: The study included 272 adolescents aged 11 to 18, who visited the pediatric endocrinologist in out-patient clinic at Children's University Hospital.
Results: The study included n=148 girls **(**54.4%) and n=124 boys (45.6%). In the study n=42 (15.4%) adolescents were smokers, boys smoked statistically more frequently 24.2% (n=30) than girls 8.1% (n=12) p< 0.001. Weight (kg) in smokers (sm) group - 108,4±15,49, non-smokers (nsm) - 101,87±16,3, r=0,18, p=0,003, p-value 0,009; height (cm) sm - 173,93±8,13, nsm - 170,03±9,93, r=0,17, p= 0,006, p-value 0.013; waist circumference (cm) sm - 113,36±13,82, nsm - 109,44±14,16, r=0,14, p=0,026, p-value 0,007; SBP (mmHg) sm - 137,17±11,13, nsm - 132,55±11,63, r=0,18, p=0,03, p-value 0,005; DBP (mmHg) sm - 85,05±10,61, nsm - 79,45±12,18, r=0,19, p=0,02, p-value 0,007; total cholesterol level (mmol/l) sm - 4,57±1,09, nsm - 4,37±0,98, r=0,04, p=0,521, p-value 0,471; LDL cholesterol level (mmol/l) sm - 3,39±0,89, nsm - 2,99±0,84, r=0,17, p=0,006, p-value 0,013; HDL cholesterol level (mmol/l) sm - 1,04±0,21, nsm - 1,16±0,29, r=0,15, p=0,012, p-value 0,010.
Conclusions: Adverse changes in the lipid profile and arterial blood pressure were found in the group of smoking adolescents with obesity. The number of smoked cigarettes per day correlates low, but statistically significant with anthropomorphic data, blood pressure, HDL and LDL levels in blood serum.

P2-d3-803 Fat Metabolism, Obesity 12

Hypothalamic obesity (HyOb) in children: a life-threatening disease

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Background: HyOb is a complex neuroendocrine disorder caused by damage to the hypothalamus. Although the mechanisms of development of HyOb are well-documented, the results of therapeutic trials are disappointing.
Objective: The aim of this report is to take attention to this life-threatening and yet untreatable condition.

Case 1: A 7 m-old girl presented with vaginal bleeding and gelastic seizures. Pituitary MRI revealed a hypothalamic hamartoma. When she was 2 y old, she had an operation because of refractory seizures. The replacement therapies for postop panhypopituitarism was given but she developed HyOb (BMI:34,6 SDS:6,5) within 3 months after the operation.Life style modification and somatostatin analogue (octreotide) was initiated without success. Since she developed severe diarrhea at 3rd month of octreotide treatment, therapeutic dose could not be achieved and had to be discontinued. When she was 3 y 9 months old, severe central apnea syndrome was detected in her sleep polysomnography, but she died before treating with noninvasive ventilation.
Case 2: A-2-y old boy with optic glioma developed panhypopituitarism after the operation and replacement therapies were started.Because of recurrences, he had to be operated three times in three years in addition to receiving chemo-and radiotherapy. Following the second operation, at 3 $^{9/12}$ y,he started to gain weight progressively and his BMI increased from 16 (SDS:0) to 36 (SDS:5,7) within 2 years. Interventions for lifestyle modification have failed. Pharmacologic therapy could not be given because of his unstable clinical condition. Unfortunately, he died of central hypoventilation syndrome at 6 y old age when his BMI was 40 (SDS:3,4).
Conclusion: The patients with HyOb are under the high risk of mortality due to central dysregulation of energy homeostasis and vital functions especially the central hypoventilation and apnea. The more effective treatment strategies are necessary for both weight gain and hypoventilation for these patients.

P2-d3-804 Fat Metabolism, Obesity 12

Altered blood pressure (BP) circadian rhythm in obese children and adolescents: an initial cardiovascular risk marker?

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Background: BP has a circadian rhythm,with a physiological drop,or nocturnal DIP.Loss of this pattern is related to cardiovascular risk and target organ damage. Ambulatory blood pressure monitoring (ABPM) demonstrates the BP circadian rhythm.
Objective: To ascertain the circadian rhythm of BP in obese children measured by ABPM and whether the change in the rhythm is related to the presence of AHT,anthropometric parameters, degree of obesity, insulin resistance, lipid metabolism, inflammatory markers, renal function and microalbuminuria.
Methods: We included 129 obese children and adolescents (74 boys, 48 prepubertal) mean age: 11.9 ± 2.5 SD.Anthropometric data, glycemia,insulin,HOMA and QUICKI indices,PCR,uric acid, lipid profile,renal function and microalbuminuria values were obtained. MAPA was performed and a AHT determined if > 25% of measurements exceeded the threshold according to normal values. The percentage of nocturnal DIP was calculated and considered normal if ≥10%.
Results: Loss of nocturnal systolic DIP was observed in 63.6%(n=82) and diastolic 54.3%(n=70). 99 patients (76.7%) had abnormal DIP; 60 were normotensive and 39 hypertensive with no statistical significance (chi-square, p=0.83).Triglycerides were significantly higher in the group with pathological Dip than group normal Dip (106.5 vs 83.8 mg/dL; p= 0.003). No significant differences were observed in anthropometric data,sensitivity and insulin resistance, inflammation or renal function.
Conclusions: A high percentage of obese patients presented an altered BP circadian rhythm (76.7%). Of the parameters evaluated only found higher levels of triglycerides in patients with pathological Dip than those with normal Dip. Other mechanisms such as sleep apnoea and/or increased sympathetic system activity may be implicated. Whether alterations in the circadian rhythm of obese children constitute a prehypertensive state and contribute to increased cardiovascular risk in this population remains to be determined.

P2-d3-805 Fat Metabolism, Obesity 12

Metabolic syndrome in children: cardiometabolic disorders and social background

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Background: Obesity epidemic demands improvement of efficacy of diagnosis, correction and prevention of continuous health disorders in overweight children.
Objective and hypotheses: It was hypothesized some staging of cardiometabolic risk development which is poorly diagnosed by the IDF criteria for metabolic syndrome (MS) in children.
Methods: History, lifestyle and psychology were studied in 961 Kharkov region adolescents. Left ventricular geometry and function, 24-hours BP monitoring, exercise tolerance, carotid intima-media thickness and metabolic peculiarities were investigated in 208 children with different degree of excess weight with further statistical comparison of the results with the IDF criteria for MS.
Results: Overweight children lifestyle is differ by more prolonged sedentary activities (4,50±1,11 vs. 2,93 ±0,08 hours in population, less regular diet 60,77±3,38% vs. 81,16±1,96 % in population. Most predictive value inherent following facts: premature birth (Se = 70%; Sp = 97%; OR = 2,54; RR = 1,93), irregular meals (Se = 39%; Sp = 81%; OR = 2,81; RR = 2,15), maternal obesity (Se = 0,36; Sp = 92%; OR = 6,34; RR = 3,41) and hypertension (Se = 73%; Sp = 66%; OR = 5,1; RR = 2,93), anxiety level and sedentary activity (MR = 0,61; F = 30,63 with P < 0,0001).
It was established the cardiovascular remodeling and dysfunction occurs in overweight already and accompanished by exercise intolerance directly linked with insulin resistance (P < 0,0001). The same time MS IDF criteria (>3) are highly specific (Sp=0,96), but low sensitive (Se=0,28) with deterioration negative predictive value (NPV=0,29).
Conclusions: There is a tendency to obesity distribution in Ukrainian population with an early cardiovascular impairment for which diagnosing more sensitive criteria are necessary. That's why cardiovascular risk prognostic scale and management strategy were offered for obese children.

P2-d3-806 Fat Metabolism, Obesity 12

Food addiction in obese children

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Background: Recently, it has been started to be emphasized that childhood obesity as in drug dependency may be dependent to compulsively too much consuming of palatable foods. In this study, frequency and property of food addiction of children in our country was investigated.
Methods: Study was carried out on 100 children admitted to Kocaeli University School of Medicine Division of Pediatric Endocrinology and Diabetes between December 2012 to June 2012. Yale Food addiction Scale (YFAS) based on DSM IV-TR was used for the evaluation of Food Addiction. YFAS criteria determines symptoms (ie, tolerance, withdrawal, loss of control etc.) of dependency for high fat and sugary foods. As application of the scale number of symptoms equaling 3 or more is expressed to be acceptance criteria. Degree of dependency is proportional to number of symptoms.
Results: Study group was composed of total 100 child and adult participants, being 37 boys, 63 girls between 10 -18 years (14.4 ±2.05).
Group was classified as 9% overweight, 7% obese and 84 % extremely obese (Girls with BMI 32.5±6.06kg/m^2, boys with 32.8±5.85 kg/m^2)
According to waist circumference percentiles referring to Hatipoğlu and friends; waist circumference of 97.7% participants was greater than 95p and 97.8% of participants rate of waist circumference to height was greater than 0.5.
71% of cases met 3 and more dependency symptoms. It was remarkable that while 17% of participants showed 3,20% showed 4, 17% showed 5, 8% showed 6 symptoms, 9% of participant showed all of the symptoms.
The most addictive foods were chocolate (70%), ice-cream (58%), fried potatoes (57%), white bread (55%), rice (53%), sweet (50%) , chips (48%), pasta

(43%), cake (35%), cookie (34%) and hamburger (34%).
Conclusions: Food addiction is very common in obese children. It is needed to have programs for prevention and treatment of obesity by reducing consumption of foods risky for food addiction.

P2-d3-807 Fat Metabolism, Obesity 12

Advanced bone age and hyperinsulinaemia in overweight and obese children

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Background: In obese children bone age (BA) tends to exceed chronological age (CA). In vitro studies in mice suggest that insulin may directly modulate skeletal growth.
Objective: To investigate a possible association between fasting insulin and BA maturation in obese children.
Methods: The study cohort comprised 74 overweight and obese children ages 4-13 years. BA divided by CA was used as an index for bone advancement. Participants were classified into tertiles based on their BA/CA ratio. Advanced BA maturation was defined as the third tertile, with BA/CA>1.21. Components of the metabolic syndrome, including fasting insulin, fasting glucose, triglycerides, and HDL levels, were also measured.
Results: Children with advanced BA were significantly younger, with higher BMI-Z, and taller than children with bone advancement at the lower tertiles. Females had a 4.7 times increased risk for advanced BA as males [95% CI (1.29-17.1); p=0.02]. Children with BMI-Z >1.96 and fasting insulin ≤ 208 pmol/L had a 3.6 increased risk of advanced BA [95% CI (1.00-12.8); p=0.02]. Moreover, hyperinsulinemia (fasting insulin > 208 pmol/L) was associated with a 6.8 fold increased risk for advanced BA independent of the degree of obesity [95% CI (1.45-32.1); p=0.01].
Conclusion: Marked hyperinsulinemia was found to be associated with advanced BA in obese children. Insulin appears to modulate skeletal growth in humans.

P2-d3-808 Fat Metabolism, Obesity 12

The associations of osteocalcin level and metabolic profile on different ethnic groups in South-West Romania

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Background: Osteocalcin is the principal component of the bone. On the other hand, the overweight and obese children associate osteoporosis.
Aim: In obese children the bone mineral density decreases. It is not know if it is a rule for all ethnic groups.
Method: 214 obese (98 boys and 116 girls) and 200 children with normal weight, between 2010-2012 were analyzed. Both groups have the same compositions on romany (group A) and non-romany children(group B). The anamnesis (born weight and height, AI), antropometric parameters (weight, height, BMI, waist circumference) were analyzed according to the age and sex. Biological tests: OGTT, fasting insulin, HbA1c, lipids with triglycerides, HDLc, LDLc (atherogenic index), vitamin D3, Ca, Ca++, alkaline phosphatase, osteocalcin (by N-MID osteocalcin) CRP and Il6. Body fat percentage was determined by Tanita body composition. DXA-osteodensitomerey was performed in children up of 12 years. No QCT was done. The dates were statically analyzed.
Results: The median age was 11.2 years in girls and 12, 5 in boys. The diagnosis of the obesity was established according to the age BMI (upper of the 95th percentiles). The CRP was elevated in all cases of the both groups. The waist circumference was greater in group B comparing to the romany. The coefficient of variations showed the inverse correlation between osteocalcin and BMI (β-0.7) or body fat central obesity for both groups The same inversely correlated with LDLc and HbA1c values for both groups romany and non-romany. The vitamin D3 level was lower in romany group than in obese non-romany children. DXA showed osteopenia more in group A comparing to the group B
Conclusions:
1. Osteocalcin is an important factor in bone metabolism
2. There are important correlations between bone metabolism and glucose/lipid metabolism in obese children
3. There are some discret differences between romany and non romany groups that needs future investigations

P2-d3-809 Fat Metabolism, Obesity 12

Adverse influence of the number of smoked cigarettes per day on blood pressure and lipid level in adolescents with obesity

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Background: The problem of smoking children and adolescents with obesity that sustains chronic inflammation in the body thereby increasing cardiovascular disease risk in adulthood is becoming progressively topical worldwide.
Objective and hypotheses: To compare anthropometric data, blood pressure and biochemical blood analyses in smoking and non-smoking adolescents with obesity and to evaluate the correlation with the number of smoked cigarettes per day.
Methods: The study included 272 adolescents aged 11 to 18, who outpatiently visited a pediatric endocrinologist.
Results: The study included n=148 girls **(**54.4%) and n=124 boys (45.6%). In the study n=42 (15.4%) adolescents were smokers, boys smoked statistically more frequently 24.2% (n=30) than girls 8.1% (n=12) p< 0.001. See the results of the study in the table.

	Smokers (mean±SD)	Non-smokers (mean±SD)	P-value	Spearman's correlation between (Cig. number)
Weight, kg	108.40±15.49	101.87±16.30	0.009	r =0.18, p=0.003
Diastolic blood pressure, mmHg	85.05±10.61	79.45±12.18	0.005	r =0.19, p=0.002
Systolic blood pressure, mmHg	137.17±11.13	132.55±11.63	0.007	r =0.18, p=0.003
HDL, mmol/l	1.04±0.21	1.16±0.29	0.013	r = -0.15, p=0.012
LDL, mmol/l	3.39±0.89	2.99±0.84	0.01	r =0.17, p=0.006

[Adverse influence of smoking]

Conclusions: Adverse changes in the lipid profile and arterial blood pressure were found in the group of smoking adolescents with obesity. The number of smoked cigarettes per day correlates low, but statistically significant with anthropomorphic data, blood pressure, HDL and LDL levels in blood serum.

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An attempt to evaluate the efficacy of psychodynamic group therapy for obese children and their families in a hospital setting

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Background: In our Clinic we offer obese children endocrinological examinations, diet and psychological support.
Objective: The aim of psychological support is to facilitate elaboration of emotions connected to obesity for children and their parents. After this period of support, in 2009 the psychologist offered the children that needed a psychotherapy and whose age was between 7-10 yrs, and their families a psychodynamic group therapy.
Methods: Seven families accepted and participated. The group lasted 2 years, with separate weekly sessions for children and for parents. Behavioural and emotional aspects in these subjects were analysed in 3 stages using Achenbach&Rescorla's Child Behavior Checklist (CBCL for 6-18yrs), a structured questionnaire to be filled in by parents. Before the beginning of the group obese children (M=3, CA 8,71±0,95 yrs, BMI 28,10±2,89) were assessed using CBCL and compared with 14 normal weight children, matched by age, sex and socio-economic status. Patients were also assessed using CBCL after 1 year and after 6 months from the end of the group therapy. In these 3 stages weight, height and BMI were measured.
Results: Obese children reported scores significantly higher than controls in scales: total (p=.004), internalizing (p=.001) and externalizing scores (p=.022), anxious/depressed (p=.0001), aggressive behavior (p=.017), social (p=.0001) and affective problems (p=.0001), anxiety (p=.005) and oppositional defiant problems (p=.019). Regarding comparisons over time, data confirm a significant decrement in the scale conduct problems (p=.041). The decrement can be observed in all the examined scales, but these differences are not statistically significant. The BMI increased after the first evaluation and decreased later.
Conclusions: Our study confirms the importance of a psychological and psychotherapeutic support for these patients. In particular, our group experience seems to be a source of change for obese children and for their parents.

P2-d3-811 Fat Metabolism, Obesity 12

Vasodilatory potential in obese children: an investigation of F-RHI using Endo-PAT

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Background: The research has been focused on the reactive hyperemia index (RHI), which can be measured quickly and simply using reactive hyperemia peripheral arterial tonometry (RH-PAT) in adults recently . RHI is corrected with a baseline correction factor, the value of which has been investigated in adults. It is unclear whether or not the Framingham RHI (F-RHI), which does not use this correction factor, can be used as an index of vasodilatory potential in children.
Objective: To investigate whether the F-RHI can be used as an index of vasodilatory potential in obese children.
Subjects: Hospital based study, subjects included 5 obese (OB) (M/F 2/3,ages 9.6±1.7) and 12 non-obese (NOB) (M/F 4/8, ages 10.4±1.9)children.All subjects provided informed consent, and the study was performed with the approval of the Ethics Committee of Kitasato University and according to the Declaration of Helsinki.
Methods: RHI and F-RHI were measured using an Endo-PAT 2000 (Itamar Medical, Caesarea, Israel).
Method of analysis: F-RHI and RHI values for the NOB and OB groups were compared using the Mann-Whitney *U* test, with the level of statistical significance set at < 5%.
Results: The level of obesity and percentage of body fat were significantly higher in members of the OB group compared with the NOB group (NOB vs OB mean ± SD) (1.9±9.2% vs 47.0±32.5%, $p< 0.01$).Comparison of F-RHI and RHI, F-RHI was significantly lower in the OB group than in the NOB group (0.173±0.226 vs -0.025±0.101 , $p< 0.05$). There were no differences in RHI between the 2 groups.
Discussion: In this study, the F-RHI values were significantly lower in the OB group compared with the NOB group. Our finding of no difference in RHI values between the 2 groups but a difference in F-RHI values suggests that use of the baseline correction factor is not appropriate in children. Thus, the F-RHI may better reflect vasodilatory potential in children than the RHI.

P2-d3-812 Fat Metabolism, Obesity 12

The prevalence of childhood obesity and central obesity in a rural Greek island and their association with gender, puberty and nationality

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Objectives: We aimed to investigate the prevalence of obesity and central obesity (CO) within children living on the small Greek island of Tinos and their associated factors.
Methods: 352 healthy children and preadolescents (54% boys) attending the primary schools of Tinos island were evaluated, aged (mean±SD) 8.53±1.72 years (range 6-11), from which 286 (81.25%) were of Greek origin and 66 (18.75%) of Albanian. Body weight, height and waist circumference (WC) were measured, plus BMI and WC percentiles were calculated. Children with WC>90th percentile were categorized as having CO.
Results: Among our patients, 235 (66.76%) were of normal weight, 88 (25%) overweight and 29 (8.24%) obese. The proportion of obesity in children (6-9.9 years) was 10.13%, yet was significantly reduced in preadolescents (11-12years) to 4.8% (p=0.050), with no gender difference. During preadolescence, the proportion of overweight was increased in boys (from 32.5% to 40.28%, p=NS), but not in girls. CO was found in 65 (18.47%) children, with a higher prevalence among the obese than overweight ones (96.43% vs 60.71%, $p< 0.001$).However foreign immigrants had lower frequency of overweight and obese children (4.55% vs 8.74%,p=0.296) and less centrally obese children (9.09% vs 20.63%, p=0.018) than the Greek participants.
Conclusions: The prevalence of childhood obesity in rural Tinos was 8.24%, which was lower than the reported national prevalence of obesity in Greece, whilst almost all of the obese and 40.91% of the overweight children presented CO. The low prevalence of childhood obesity and CO on this small island could possibly be attributed to a more healthy diet and natural way of life.

P2-d1-813 GH and IGF Physiology and Treatment 4

Oxygen-transporting properties of erythrocytes and the blood antioxidant system in children with growth hormone deficiency and girls with Turner syndrome

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Background: The differences oxygen-binding properties of erythrocytes and oxidative stress in prepubertal untreated children with growth hormone deficiency (GHD) and girls with Turner syndrome (TS) were observed.
Objective and hypotheses: The development of tissue hypoxia and increase the amount of free radicals due the metabolic disorders leads to a change in the properties of hemoglobin in erythrocytes and antioxidant system of blood. The aim of our study was to examine oxygen-transporting properties of erythrocytes and blood antioxidant system conditions in untreated prepubertal children with GHD and girls with TS.
Methods: 11 prepubertal children with GHD (9 boys; aged 4-9 yr, median 7.6 yr) and 12 prepubertal girls with TS (aged 12-14 yr, median 13.2 yr) were included in the study. All of them have not been treated with GH before. The data of 9 prepubertal children (7 boys; aged 5-7 yr, median 5.9 yr) used as control. The properties of hemoglobin in erythrocytes were examined using Raman spectroscopy. Blood antioxidant system was examined using activity of superoxide dismutase, catalase and ceruloplasmin level and total antioxidant capacity of plasma evaluated by FRAP.
Results: The oxygen-binding properties of erythrocytes in children with GHD differed significantly from control data (levels of oxyhemoglobin, NO-hemoglobin and the ability of hemoglobin to reset oxygen were significantly elevated - by 55%, 50% and 28% respectively). Same parameters in girls with TS didn't significantly differ from control data. Values of total antioxidant capacity of plasma in GHD children and in girls with TS were significantly lower than those in control data (60% and 34% respectively). Level of ceruloplasmin in children with GHD and TS was elevated (about 40%).
Conclusions: We interpreted these results as mild oxidative stress development in untreated children with GHD and TS and also the presence the tissue hypoxia in GHD children.

P2-d1-814 GH and IGF Physiology and Treatment 4

Effects of GH treatment on oxygen-transporting properties of erythrocytes and blood antioxidant system in girls with Turner syndrome

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Background: The effects of growth hormone (GH) therapy on the oxygen-binding capacity of erythrocytes and oxidative stress in prepubertal girls with Turner syndrome (TS) were observed.
Objective and hypotheses: The oxygen-transporting properties of erythrocytes and blood antioxidant system could be used as markers of overall condition of patients. The aim of our study was to examine the effects of GH-therapy on the condition of girls with TS using oxygen-trasporting properties of erythrocytes and the state of the blood antioxidant system as markers
Methods: 12 prepubertal girls (aged 12-14 yr; median 13.2 yr) with TS were included in the study. All of them have not been treated with GH before. The data of 9 prepubertal children (2 girls, 7 boys; aged 5-7 yr; median 5.9 yr) used as control. Properties of hemoglobin in erythrocytes were examined with the use of Raman spectroscopy. Blood antioxidant system was studied by measuring the activity of superoxide dismutase, catalase and ceruloplasmin level and total antioxidant capacity (TAC) of plasma evaluated by FRAP. All parameters were measured before and after 6 months of GH treatment (0.05 mg/kg/day).
Results: The properties of hemoglobin did not significantly differ from control data and did not change significantly during 6 months of therapy. The ability of hemoglobin to bind oxygen was an exception for it was significantly lower than control data (about 18%). The value of TAC of plasma was significantly lower than that of control data (about 34%), but did not significantly change during treatment. Levels of ceruloplasmin before treatment was elevated in comparison to that of control data (about 40%) and decreased to normal levels after 6 months of therapy.
Conclusions: This study suggests that oxygen-binding properties of hemoglobin do not change significantly in girls with TS. However, mild oxidative stress was detected before treatment which subsided during GH-therapy.

P2-d1-815 GH and IGF Physiology and Treatment 4

A novel nonsense mutation at carboxyl terminal region of *IGF-1R* (p.Q1220X) causes reduction of the IGF-1R protein, and results in SGA short stature

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Background: The insulin-like growth factor (IGF) plays key roles in intrauterine fetal growth and postnatal growth through the IGF-1 receptor (IGF-1R). Heterozygous *IGF-1R* mutations presenting with short stature were observed including our patient (Kawashima Y, 2005).
Objective: The purpose of this study was to elucidate the effect of the novel heterozygous mutation (p.Q1220X) on IGF-1R.
Patient and methods: Patient was an 8-year-old Japanese boy, who was born at 40 weeks of gestation, with a birth weight of 2,228 g (-3.3 SD), birth height of 46 cm (-2.1 SD). His height was 113.6 cm (-2.7 SD) at the age of 8 years, 9 month. He had no family history of short stature.
R^- cells, which are 3T3-like mouse embryo cells with targeted disruption of the IGF-1R genes, were transfected with the mutated or wild-type IGF-1R gene, and the expression of IGF-1R protein was evaluated by a Western Blot assay. The expression of IGF-1R mRNA was compared by use of semi-quantitative RT-PCR after transfected R^- cells were harvested with emetine which inhibits nonsense -mediated mRNA decay (NMD).
Results: We identified heterozygous mutation (p.Q1220X) of the *IGF-1R* gene in an 8-year-old Japanese boy with SGA short stature. His parent and brother were not identified the mutation (p.Q1220X). The cells transfected with mutated IGF-1R gene showed an extremely reduced IGF-1R protein.
The cells transfected with the mutated IGF-1R gene treated with emertine showed no difference in the amount of mutant IGF-1R mRNA compared that without emertine.
Furthermore, we are going to study the autophosphorylation of mutated IGF-1Rb, which is able to express.
Conclusions: The cells transfected with mutated IGF-1R gene showed an extremely reduced IGF1R protein, and the reduced IGF1R protein is considered to cause a growth failure in our patient.

P2-d1-816 GH and IGF Physiology and Treatment 4

A precocious GH peak at GHRH plus arginine test in GH sufficient short children is predictive of a lower growth velocity

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Background: In children, GH secretion is considered sufficient when at least one value is >20 ng/mL at the GHRH + Arginine (ARG) test. Because GH typically peaks at 45 minutes, we evaluated whether peak occurrence at one specific time is predictive of clinical outcomes in short stature children who are GH sufficient.
Methods: Children who performed a GHRH plus ARG test for short stature were retrospectively recruited. Inclusion criteria were:
1) a GH peak > 20 ng/ml;
2) Tanner stages within 1-3 stages;
3) 1 year growth velocity since the test execution;
4) born adequate for gestational age;
5) the absence of signs suggestive of syndromes.
Primary outcomes were height standard deviation score (SDS), growth velocity (GV), GVSDS and IGF-I SDS.
Results: 228 subjects were recruited, by which 14 were excluded because they did not satisfy inclusion criteria. Of 214 subjects, 121 (56.5%) had a peak at 45' min, 55 (25.7%) at 30' min, and 38 (17.8%) at 60' min. Subjects presented a peak at 30 min had lower height SDS ($p < 0.05$), growth velocity ($p < 0.001$), growth velocity SDS ($p < 0.001$), and GH peak ($p < 0.05$) than those had a peak at 45' min. Subjects presented a peak at 30' min had lower GV ($p < 0.001$), and GVSDS ($p < 0.001$), but higher GH peak ($p < 0.05$) than those had a peak at 60' min. No differences were shown between children with a peak at 45' or 60' min. No differences in Tanner stages, sex, IGF-I SDS were recorded among three groups.
Conclusions: A peak at 30 minutes at the GHRH + ARG test in children who are short and without GH deficiency may be predictive of lower growth velocity in the year of the test. Because arginine infusion stops at 30 minutes, a somatostatinergic higher tone could have a role in the clinical picture.

P2-d1-817 GH and IGF Physiology and Treatment 4

Evaluation of asymmetric dimethylarginine (ADMA) levels in children with growth hormone deficiency

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Background: Asymmetric dimethylarginine is an endogenous nitric oxide synthase inhibitor. The decrease of nitric oxide due to the increased ADMA, leads to endotelial dysfunction.The effects of growth hormone deficiency (GHD) that lead to cardiovasculer system dysfunction and dyslipidemia are also well- known.
Objective: It was aimed to investigate the levels of ADMA in isolated growth hormone deficiency.
Material and methods: 31 patients diagnosed with GHD who were not in treatment and 29 age- sex matched healthy children enrolled into the study. Fasting IGF-1(insülin like growth factor-1), IGFBP-3(insülin like growth factor binding protein-3), glucose, insulin, lipid profile were analyzed and HOMA-IR values were calculated. ADMA levels were studied by ELISA method.
Results: The mean age of the patients was 12.5±1.8(8.5-16.5) years. 19 were male, 12 were female. 11 of the cases were pre-pubertal and 20 of the cases were pubertal. The mean age of the control group was 11.5±2,1(7.3-16.6) years. 18 were male and 11 were female. 8 cases were prepubertal and 21 cases were pubertal. It was not found any difference of ADMA levels between patients and controls. It was not found any relationship between ADMA levels and age, gender, pubertal status. There were not any significant relationships between ADMA and glucose, insulin, HbA1c, HOMA-IR values in the GHD cases. Positive correlation between ADMA and HbA1c was determined in the control group. It was not found statistically significant relationships between ADMA and total cholestrole, triglyceride values in all two groups. ADMA was positively correlated with LDL(low density lipoprotein); although ADMA was negatively correlated with HDL(high density lipoprotein) in the GHD cases.
However, there were not any correlation between ADMA and HDL, LDL values in the healthy children.
Conclusion: It was shown that serum ADMA levels of the children with isolated growth hormone deficiency were not different from those of healthy children.

P2-d1-818 GH and IGF Physiology and Treatment 4

Birth seasonality in Japanese patients with growth hormone deficiency

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Background: Although the birth seasonality has been reported in various pediatric endocrine diseases, such as congenital hypothyroidism and type 1 diabetes, it has not been studied in growth hormone (GH) deficiency (GHD).
Methods: We analyzed birth months of 979 Japanese patients with severe GHD. The diagnosis was based on the low peak levels of serum GH (< 3.0 ng/mL) in at least two provocative tests and low levels of serum IGF-1 (< 150 ng/mL). Patients having combined pituitary hormone deficiencies, chromosomal abnormalities, or other congenital diseases were excluded from the present study. Differences in the distribution of birth months were investigated between the patients and the Japanese general population obtained from 15,680,228 individuals for the years 1997-2010. Statistical differences were examined by the Walter and Elwood method.
Results: We found a significant deviation of birth months in patients with severe GHD (p = 4.28E-06). A peak of birth frequencies was observed in November with the ratio of observed-to-expected births (O/E ratio) of 1.34, and a trough was found in April with an O/E ratio of 0.67. Births of the Japanese general population were almost equally distributed among the 12 months.
Conclusions: These results indicate that pre- or peri-natal exposure to some seasonally-varying environmental factors may facilitate the development of GHD. Further studies are necessary to identify environmental factors that affect GH secretion.

P2-d1-819 GH and IGF Physiology and Treatment 4

Effect of long-term growth hormone therapy on adult height in children born small for gestational age

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Background: Recombinant human growth hormone (r-hGH) is used to treat children born small for gestational age (SGA) who have not demonstrated catch-up growth. Few studies have explored long-term treatment effects.
Objective and hypotheses: To assess the effect of r-hGH on adult height in children born SGA.

Methods: Children born SGA who received 2 or 3 years of prior r-hGH treatment (0.067 mg/kg/day, the approved dose in France at the time) in two Phase III trials, and ≥1 year of post-treatment observation were enrolled in an extension study. During the extension study, children were observed (untreated) or re-treated (0.067 mg/kg/day), until adult height was reached.
Results: Ninety-one children were enrolled in the extension study; 68 achieved adult height (22 observed, 46 re-treated). Mean (standard deviation) age was 4.0 (1.8) years at start of prior treatment and 10.3 (2.5) years at start of re-treatment. At end of prior treatment, median (range) height standard deviation score (HSDS) was -1.56 (-3.5, 0.2) for observed children and -2.22 (-4.9, -0.4) for re-treated children. Total treatment duration (prior and re-treatment) was 2.0-3.1 years for observed children and 3.4-12.6 years for re-treated children. Median (range) target heights (cm) were similar in the re-treated and observed groups (165.0 [151; 182] vs 166.8 [146; 183]). Median (range) change in HSDS from start of prior treatment to last assessment was 1.48 (-0.3, 2.9) in re-treated children and 0.65 (-0.5, 2.5) in observed children (p=0.002). Overall, 56.5% (26/46) of re-treated children reached an adult height within the range of their peers (HSDS≥-2), compared with 36.4% (8/22) of observed children.
Conclusions: Children born SGA who received prior treatment with r-hGH and were re-treated achieved significantly greater improvements in HSDS than children who were not re-treated. These data support the use of r-hGH until adult height is reached.

P2-d1-820 GH and IGF Physiology and Treatment 4

Growth hormone improves short stature in children with Diamond-Blackfan anemia

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Background: Diamond-Blackfan anemia (DBA) is an inherited hypoplastic anemia syndrome with risk for development of aplastic anemia, MDS/leukemia, and other malignancies. Steroid therapy is a mainstay of treatment, with resultant short stature. Isolated cases have demonstrated improved growth on growth hormone (GH) therapy.
Objective and hypotheses: Treatment with GH will improve linear growth in DBA.
Methods: GH treatment data were obtained from 6 children with DBA at our site and from 13 children in the Genentech National Cooperative Growth Study database. Control data from 65 non-GH treated children were obtained from the National DBA Registry. Annual growth velocity (GV) and height-for-age Z-scores (HAZ) were compared between the groups and over time for up to 4y of GH treatment.
Results: Examination of constructed DBA-specific male and female height for age charts for non-GH treated patients revealed short stature compared to the CDC normal charts. GH-treated patients had significantly lower HAZ immediately prior to treatment initiation (baseline) compared to non-treated patients. Among GH-treated patients, annual GV significantly improved in the first two successive years relative to pre-treatment GV. In addition, HAZ significantly improved in each of the 4y of GH therapy compared to baseline. After 2y of therapy, HAZ for GH-treated patients were not statistically significantly different from controls, demonstrating successful catch up growth.
Conclusions: GH treatment in children with DBA improves both GV and HAZ during treatment sustained for up to 4y. Very short children with DBA can be treated successfully with GH to restore stature to levels comparable to less affected patients. The DBA height charts are useful tools for assessing age-specific growth in this typically short population. Careful consideration of individualized benefit versus risk is important in view of long-term underlying ~5% malignancy risk in DBA.

P2-d1-821 GH and IGF Physiology and Treatment 4

Growth hormone devices changeovers: causes and effects

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Background: Although the benefits of free patient choice for patients commencing GH therapy are recognised in terms of adherence and also height velocity, no data exists on changeovers for existing GH-treated patients.
Methods: Retrospective analysis of patient GH changeovers since 2000.
Results: There were 127 changeovers (110 patients; 57 female) of GH device in our unit; with 2 device changeovers in 11 patients and three in 2. Changeovers were: needled device→needled (N=63), needled→needle-free (24), needle-free→needled (38), needle-free→needle-free (2). Reasons for changing were related to: injection (pain, bruising, leakage, needle/needle-free: N=28), device (ease of use/independence, new device, breakage, dosing, refridgeration, noise (82)), poor adherence (17), study trial (12) and GH supply (2). 25 patients (22.7%) changed GH device within a year of starting GH. In those changing device after GH therapy for >1 year growth data were available in 50 patients at time of device change and also for >1 year before and after changeover. Overall mean(SD) height velocity (HV) was 5.94(2.36)cm/y pre-change and 5.80(2.23)cm/y post- (NS), with corresponding mean(SD) HVSDS from 1.15(2.61) to 1.65(2.66) (NS). In those patients growing slowly (HV < 4cm/y (N= 11) or HVSDS < 0 (N=17)) whilst there was a statistical improvement in height velocity (p= 0.02 for HV and p< 0.01 for HVSDS), only a minority achieved an acceptable height velocity post-change (HV >5cm/y (36%) or HVSDS >1.0 (41%)). In those growing with a HV >4cm/y there was a statistical fall in mean(SD) HV from 6.92(1.78) to 6.20(2.07)cm/y (p=0.03), but not HVSDS.
Conclusions: Existing GH-treated patients change device for various reasons. Unlike new patients there is not consistent evidence that changing GH device is associated with improved GH adherence (assessed using height velocity). In addition, in the majority of patients who are not adherent with therapy, changing GH device does not appear to improve adherence.

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Is there any evidence that GH increases the risk to develop leukaemia in children treated for malignant tumors?

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Background: Children surviving cancer have an increased risk for a second malignant neoplasm (SMN) and the risk is further increased by GH substitution. During nine years of follow-up including 4.6 years on GH, 20 malignant neoplasms were reported (incidence 6.4/1000).No case of leukemia was reported (Ergun-Longmire et al JCEM 91:3494-98,2006) .
Objective: Is there an increased risk to develop leukemia as a SMN during GH substitution?
Methods: Normative data on incidence of leukemia in children surviving a malignant neoplasm was estimated on data from Childhood Cancer Survivor Study (CCSS ,Neglia et al J Natl Cancer Inst 93:618-29,2001).Incidence in children treated with GH was estimated from KIGS (Pfizer International Growth Database) and NCGS (National Cooperative Growth Study,Bell et al JCEM 95:167-77,2010). The confidence intervals for the rate ratios have been calculated according to Rothman et al Modern epidemiology 3rd ed.2008.
Results: KIGS. In 3647 children with GHD after treatment of malignant neoplasms and on GH substitution for a median duration of 3.9 years, one case of leukemia (AML) developed after 0.7 years on GH in a girl with NF-1 treated for medulloblastoma.
NCGS. In 2500 children with GHD after treatment of a malignant neoplasm and on GH for a mean of 4.3 years five cases of leukemia were reported.
CCSS. 13,581 children treated for a malignant neoplasm and surviving at least five years were observed for a median of 15.4 years (total 140,792) and 24 cases of leukemia were reported (incidence 0.17/1000).
Relative risk evaluation: The incidence of leukemia (0.24) in the GH treated children (n=6) was not statisticly significantly increased compared with the incidence in CCSS, rate ratio 1.4 (95th CI 0.57-3.44).
Conclusions: No clear evidence that GH increases the risk to develop leukemia. as a second malignant neoplasm.

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Quality of life in adolescents and young adults with childhood-onset growth hormone deficiency (COGHD)

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Background: Reports on quality of life (QoL) in adolescents and young adults with COGHD are scarce. Moreover, QoL in patients with partial COGHD have not been assessed previously.
Objective and hypotheses: The aim of the study was the evaluation of QoL in adolescents and young adults with COGHD who stopped the treatment with recombined human growth hormone (rhGH) after final growth achievement.
Methods: We used the licensed Polish versions of general (SF-36 v.2) and specific for the disease (QoL - AGHDA) questionnaires to evaluate QoL in in a group of total 122 subjects aged 16-25 years. Based on current peak serum GH concentrations in insulin tolerance test patients were qualified for one of the following groups:
1) severe growth hormone deficiency - GHD (peak GH< 5.0 ng/ml, n=26);
2) partial growth hormone deficiency - PGHD (peak GH 5.0-10.0 ng/ml, n=22);
3) normal growth hormone secretion - NGH (peak GH>10.0 ng/ml, n=28);
4) healthy subjects - H (n=46).
Results: SF-36 v.2 Physical Component Score (PCS) (50.9±2.7), Physical Functioning (PF) (51.8±3.6) and Role Emotional (45.8±4.7) in GHD patients were significantly lower ($p< 0.05$) than in NGH (51.3±2.2; 56.0±4.2 and 54.0±5.2; respectively) or H (54.4±1.4; 56.0±0.4 and 51.4±2.1; respectively). Also General Heath (GH) (45.8±5.2) in GHD was lower ($p< 0.05$) compared to other examined subjects (PGHD 51.9±3.3; NGH 50.9±3.1 and H 52.5±2.1), but Mental Component Score (MCS) was similar in all examined groups. The assessment with QoL-AGHDA showed significantly lower ($p< 0.01$) QoL in GHD (7.2±1.2) than in NGH (4.0±0.4) or H (3.0±0.3). There were no differences in QoL-AGHDA scores between PGHD, NGH and H subjects.
Conclusions:
1. Some aspects of QoL in adolescents and young adults with COGHD are disturbed in comparison with COGHD patients with current normal GH status and healthy controls.
2. QoL in adolescents and young adults with COGHD and partial growth hormone deficiency in transition period is normal.

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Changes of male prevalence in the treatment observed during the GH era within KIGS

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Background: There is a gender disparity in favour of male children treated with rhGH. It remains unclear whether this is due to the natural prevalence of growth disorders or is a result of social and cultural biases.
Objective: We aimed to investigate the characteristics of male and female children treated with GH from various regions and with different diagnoses. This segment of the study is focussed on the examination of the male-to-female ratio over 20yrs.
Methods: The retrospective analysis is based on data from KIGS (Pfizer International Growth Study), a survey conducted between 1990 an 2010 the results (% males) and numerical trends were calculated according to
a) diagnoses: idiopathic GHD (IGHD), congenital and acquired GHD in all regions, and
b) geographical regions in IGHD:
1) Europe
2) Japan
3) USA
4) "Rest" of world (RoW).
Results: The results, which are the first part of a larger gender study, are listed in the Table.

	Year	All Years		1990	1995	2000	2005	2010	Numeric trend
	Region	N				% Males			
IGHD	All	37062	67.2	70.0	67.6	67.0	65.9	64.7	+
Cong. GHD	All	3476	63.6	65.0	64.5	60.8	65.4	63.2	no
Acq. GHD	All	5436	59.5	60.3	59.9	59.7	56.8	59.9	no
IGHD	Europe	21939	65.2	69.5	67.0	63.0	64.0	62.9	+
IGHD	Japan	6430	67.6	70.1	68.5	64.7	61.8	68.0	(+)
IGHD	USA	7458	72.9	69.1	73.5	73.1	73.3	71.5	no
IGHD	ROW	3489	64.9	78.7	55.8	60.9	63.6	62.5	+

[Table 1]

There is an excess of males treated with GH particularly in IGHD, less so in congenital and acquired GHD where no diminishing trends are observed. While there is a general trend towards a decrease in the male quota in IGHD this is not the case in the USA or Japan.
Conclusions: There is a persisting male predominance in the treatment of IGHD - and other disorders - but with major quantitative differences between regions. The potential factors (e.g. social, cultural, economical) associated with these differences need to be uncovered in order to assure equal benefits of GH treatment for short females.

P2-d2-825 GH and IGF Physiology and Treatment 5

Safety and effectiveness of Increlex® therapy in children enrolled in the Increlex Growth Forum Database (IGFD) in Europe: 3 years interim results

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Background: The post-authorization registry, European Increlex® (Mecasermin [rDNA Origin] Injection) Growth Forum Database (EU-IGFD) started in Dec 2008 to collect data on children with growth failure treated with Increlex®.
Objective and hypotheses: To report 3-yr safety and effectiveness data.
Methods: Multicenter, open-label observational study.
Results: As of Oct 2012, 166 patients were enrolled in 9 countries: 34% female, 84% with severe primary IGF-1 deficiency, 80% pre-pubertal, 67% growth treatment-naïve. Median age at first injection was 10.8 yr. Mean [95% CI] treatment duration was 709 [638 ; 779] days. Median dose was 40, 113, 120 and 113 µg/kg BID at treatment initiation, yr 1, 2 and 3 respectively. Effectiveness data are summarized by mean (SD) of height and Δheight SDS.

	n*	Height SDS	n*	Δheight SDS
All pts (n=166) Baseline	148	-3.54 (1.37)		
Yr 1	115	-3.17 (1.36)	110	0.33 (0.40)
Yr 2	70	-3.08 (1.62)	65	0.57 (0.65)
Yr 3	39	-2.88 (1.90)	35	0.60 (0.60)
Treatment-naive pre-pubertal pts (n=91) Baseline	84	-3.33 (1.38)		
Yr 1	53	-2.77 (1.18)	50	0.46 (0.36)
Yr 2	26	-2.75 (1.48)	24	0.80 (0.62)
Yr 3	10	-2.46 (2.07)	9	0.68 (0.54)

*[*n data available at the timepoint]*

No new safety concerns were reported. Targeted adverse events were reported for 58 pts (37%), the most frequent (≥5% of pts) being hypoglycaemia (15%), lipohypertrophy (9%), tonsillar hypertrophy (8%) and headaches (5%). Hypoglycaemia did not appear to be related to treatment dose or duration and tended to be more frequent in girls, in pts with history of hypoglycaemia and with Laron syndrome (OR [95% CI] = 2.2 [0.9; 5.2]; 2.6 [0.6; 11.1] and 2.1 [0.8; 6.3] respectively).
Conclusions: The results did not show any new safety signals. Hypoglycaemia was the main adverse event. Despite the late treatment start, the heterogeneity and the small sample size, a clear increase of height SDS was observed under treatment.

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Low vitamin D levels affect height velocity in growth hormone deficient (GHD) children treated with growth hormone (GH)

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Background: Children with GH deficiency receiving GH treatment show a broad response.
Objective and hypotheses: To evaluate whether vitamin D levels interfere with growth response in GHD children receiving GH treatment.
Methods: Fifty three GHD children {mean age (SD 12.1 (3.3) years; 28 boys, 42 prepubertal who were under treatment with GH (24 microg/kg daily) for a median duration of 2.5 years (range 0.43-10.5) were studied. A 4-day diet assessment was performed and analysed using the Science Technology Diet 200A Advanced Edition Software. Total 25OH vitamin D, PTH, calcium, phosphorus, alkaline phosphatase were measured. Weight, height, Body mass index (BMI), BMIz-score, height velocity (HV), HVSDS, were evaluated at regular intervals since initiation of GH treatment. HV/HVSDS was considered low if it was below 25th CE at the time of vitamin D evaluation and sufficient if it was >25th CE. Both groups were comparable in age, duration of GH treatment and pubertal status. IGF-I and lipid profile were measured.
Results: Vitamin D levels were significantly lower in 14/53 patients with HVSDS < 25th CE [mean SD 18.02(6.9) vs 27.4(13.3) ng/ml p=0.002)]. No difference was found between the two groups in energy or macro nutrient intake, in PTH, calcium, phosphorus or alkaline phosphatase levels. No differences were found in other micronutrients or elements. BMI was comparable between the two groups. From 15 children with abnormal vitamin D levels who were further evaluated with DEXA, 9 had osteopenia and 2 osteoporosis.
Conclusions: This pilot study shows that vitamin D intake may be important in children with GHD, in order to achieve a good growth response to GH treatment.

P2-d2-827 GH and IGF Physiology and Treatment 5

Management of childhood-onset growth hormone deficiency in young adulthood

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Background: Adolescents with childhood onset GH deficiency (CO-GHD) may require re-evaluation of their GH axis on attainment of final height as not all CO-GHD patients remain GH deficient (GHD).
Aim: Retrospective review of management of young adults with CO-GHD in two Scottish tertiary paediatric centers.
Population: 104 CO-GHD patients (M:65), median (range) age 21(16-35) yrs who had attained final height between 2005 and 2012 were reviewed. Categories of GHD included: congenital n=29/104(27.8%); acquired n=51/104 (49%); and idiopathic/associated with other chronic diseases n=24/104 (23%), of whom n=63/104 (60.5%) had Isolated GHD whereas n=41/104 (39.4%) had Multiple Pituitary Hormone Deficiency (MPHD). Median age at CO-GHD diagnosis was 11.2yr (0.3 -16.6) with initial GH peak 2.2µg/l (0.1 - 6.5); and initiation of GH therapy at 9.5 (0.4 -16.9) yrs.
Result: At final height, n=60/104(57.6%) CO-GHD adult were re-evaluated at a median age 18.2 yr (15-27.5), 0.5 (0.1-12) years after withdrawal of GH therapy at age 16 (9 -21) yr. Median duration of treatment was 7.6 (0.4-16.3)yr. At retesting median GH peak was 1.7µg/l (0.1-23.7) and IGF1 level 79ug/l (15-560). Of those re-evaluated 52/60(86.8%) remained GHD and were eligible for adult GH replacement, with 45/60(75%) re-starting GH and 7/60(11.6%) declining GH. The remaining CO-GHD treated patients n=44/104(42.3%) were not re-evaluated either because they were transferred to adult services without re-evaluation (n=21), stopped treatment without re-evaluation (n=6), were lost to follow up while on treatment (n=10), or had missing data in (n=7).
Conclusions: A substantial proportion of CO-GHD patients remain GHD and most opt for GH therapy as adults, yet not all are re-evaluated. A consensus standardised pathway for re-evaluation of the GH axis between paediatric and adult services has not yet been reached. There is a need to study the current practice of assessment and management of CO-GHD in the UK.

P2-d2-828 GH and IGF Physiology and Treatment 5

A population pharmacokinetic and pharmacodynamic model following a phase II study of MOD-4023 in growth hormone deficient adults supporting the assessment of pharmacokinetic and pharmacodynamic in growth hormone deficient children

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Background: PROLOR Biotech's long-acting hGH (MOD-4023) may obviate the need for the numerous injections now required for the treatment of growth hormone deficiency (GHD). This technology is based on a natural peptide, the C-terminal peptide (CTP) of the beta chain of human chorionic gonadotropin (hCG) which provides hCG with the required physiological longevity. During Phase II study in GHD adults a PK/PD model was developed in order to characterize the correlations between the MOD-4023 injected dose, blood concentrations and IGF-1 response. Based on this model, sparse sampling approach for PK/PD for Phase II in GHD children was adopted. The model will be used for PK/PD analysis during pediatric Phase II clinical study.
Methods: A sequence of nested PK models was generated to choose the optimal PK model. The final base model was a two compartment model with an extravascular compartment and Tlag. A full population PK/PD covariate analysis was performed using the forward/backward covariate deletion method which evaluated sex, age, height, weight and initial r-hGH dose as potential covariates, reveling a statistically significant relationship between BMI and EC50
Results: External validation showed the ability of the model to properly predict for each patient the IGF-1 levels based on Bayesian estimates. In addition, PK/PD results from Phase 1 were simulated, permitting evaluation of their suitability to the data. The model was able to fit the individual MOD-4023 and IGF-1 data.Finally, the established model was used to predict the population time profile of IGF-1 for naïve GHD adult patients administered with MOD-4023 on weekly basis.
Conclusions: Based on the existing data, the established model is precise and potentially predictive. It might be used to support PK/PD analysis following sparse sampling in pediatric GHD population during Phase II study and to potentially correlate between administered dose and height velocity in this study.

P2-d2-829 GH and IGF Physiology and Treatment 5

Two-year safety and efficacy data from PAtients TReated with Omnitrope® (PATRO) children − a multi-centre, non-interventional study in infants/children/adolescents requiring growth hormone treatment

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Background: PATRO Children is an international, open, longitudinal, non-interventional study of the long-term safety and efficacy of Omnitrope®, a biosimilar recombinant human growth hormone (rhGH).
Objective: The primary objective is to assess the long-term safety of Omnitrope®, particularly the diabetogenic potential of rhGH, the risk of malignancies, and potential risks of rhGH therapy in Prader-Willi syndrome. The long-term efficacy of Omnitrope® is a secondary objective.
Population and methods: PATRO Children includes infants, children and adolescents who are receiving treatment with Omnitrope® according to country-specific prescribing information. To evaluate safety, all adverse events (AEs) are monitored and recorded. Laboratory values (including glucose metabolism and anti-hGH antibodies) are requested at least once a year. To evaluate efficacy, height standard deviation score (HSDS), height velocity (HV) and HVSDS are derived from height measurements and country-specific reference tables.
Results: To date, 1837 patients have been recruited from 184 sites across 10 countries. The mean treatment duration is 17 (range 0.03−73.36) months. There have been no cases of new-onset diabetes in any patient or of anti-hGH antibodies in patients tested so far (n=69). In total, 88 patients (4.8%) have experienced treatment-related AEs and 38 (2.1%) have experienced a serious AE. SAEs were treatment-related in 2 (0.1%) patients. There have been no reports of rhGH-related malignancies and no additional safety concerns. Efficacy data at 2 years indicate a positive effect of Omnitrope® on HSDS (Δ+1.1), HV (7.3 cm/year) and HVSDS (Δ+2.6) in naïve patients with growth hormone deficiency.
Conclusions: This 2-year analysis shows that Omnitrope® was safe and well tolerated in a wide range of paediatric indications. Omnitrope® was effective in the majority of children. This ongoing study will extend the evidence base for Omnitrope®, and rhGH in general, in paediatric indications.

P2-d2-830 GH and IGF Physiology and Treatment 5

One month change in Insulin-like growth factor binding protein 3 (IGFBP3) consistently associates with changes in growth markers from year one to five of recombinant human growth hormone (r-hGH) treatment in short children with GH Deficiency (GHD) but not with Turner syndrome (TS)

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Background: Monitoring serum levels of insulin-like growth factor (IGF)-I and IGFBP3 levels can be used to individualize dosing of r-hGH therapy. The PREDICT long-term follow-up study has investigated short-term changes in serum biomarkers and long-term growth in children receiving r-hGH.
Objective and hypotheses: Assess IGFBP3 and IGF-I as potential early markers for growth response to r-hGH up to year (Y) 5 of treatment.
Methods: Prepubertal, treatment-naïve girls with TS and short children with classic idiopathic GHD were included. Correlations (Spearman's) between changes in (Δ%) IGF-I & IGFBP3 at Month (M) 1 and auxological markers (from baseline [BL] at each year [Y], i.e. BL-Y1,-Y2,-Y3,-Y4&-Y5), were assessed in the intention-to-treat (ITT) cohort.
Results: Numbers of children in the ITT cohort at BL, M1, Y1, Y2, Y3, Y4 & Y5 were 149, 147, 70, 59, 67, 66 & 55, respectively for TS and 169, 166, 118, 114, 115, 105 & 89 for GHD. Median annual r-hGH doses were: TS, 48-51 µg/kg/d; GHD, 30-35 µg/kg/d. In TS no correlations were observed between M1 ΔIGFBP3 or IGF-I and yearly Δ auxological parameters. In GHD, M1 ΔIGF-I was significantly correlated with only Δ height (ht) standard deviation score (SDS) at Y1 (Δ%, r=0.258). The table shows correlations between M1 ΔIGFBP3 (%) and changes from baseline (CFB) of growth markers over the 5 years of treatment (r-value, all p< 0.05).

ΔIGFBP-3 (%)	CFB at year 1	CFB at year 2	CFB at year 3	CFB at year 4	CFB at year 5
Δ height SDS	0.291	0.241	0.250	0.299	0.283
Distance to target height SDS	0.319	0.264	0.258	0.309	0.278
Δ weight SDS	0.380	0.402	0.430	0.431	0.395

[Table]

Conclusions: In children with GHD, M1 ΔIGFBP3 is associated with Δ height SDS, distance to target height SDS and Δ weight SDS in response to r-hGH treatment over 5 years, indicating the importance of the initial change in IGFBP3 as a marker of longer term growth response.

P2-d2-831 GH and IGF Physiology and Treatment 5

Baseline (BL) characteristics of GH-treated patients (pts) enrolled in the prospective genetics and neuroendocrinology of short stature international study (GeNeSIS): trends over time

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Background: As a prospective observational study of childhood growth disorders, GeNeSIS provides the opportunity to explore changes over time in patient & treatment characteristics.
Objective: To assess trends in BL characteristics over time by diagnosis (dx) group (gp): GH deficiency (GHD), idiopathic short stature (ISS), Turner syndrome (TS), small for gestational age (SGA) & by geographic region (all diagnoses combined): Asia Pacific (AP), Eastern Europe (EEU), Japan (JP), USA, Western EU (WEU).
Methods: Statistical analyses were performed by year of enrolment (1999-2010) for pts GH naive at BL.
Results: Significant trends over time for older age at dx & initiation of GH were seen for GHD, but no trend (+ or -) was seen in any other dx (Table). Significant increases in BL height (Ht) SDS were seen for all dx gps, while BMI SDS increased for GHD & SGA only. BL GH dose increased significantly over time for GHD, TS & SGA, but not ISS. Peak stimulated GH (GHD & ISS) did not vary (data not shown).
Little clinically relevant change in BL characteristics over time was seen across regions, apart from BL Ht SDS, which increased in EEU, JP, USA & WEU (r=0.19, 0.07, 0.15 & 0.12; p< 0.02). In USA & WEU small increases were seen for age at dx & GH initiation (USA: r=0.08 [both], p< 0.001; WEU (r=0.06 & 0.07, p< 0.001).

Variable (r, p, [range of annual means; min/max])	GHD (N=6903)	ISS (N=1394)	SGA (N=547)	TS (N=804)
Age at diagnosis of growth disorder (year)	0.12, <0.001 [7.6/10.5]	-0.02, 0.498 [9.1/11.1]	0.05, 0.206 [6.5/10.4]	0.02, 0.635 [7.4/9.2]
Age at start of GH (year)	0.11, <0.001 [8.1/10.9]	-0.01, 0.796 [9.2/11.9]	-0.02, 0.677 [8.1/10.7]	0.00, 0.972 [8.7/10.4]
Baseline height SDS	0.17, <0.001 [-2.9/-1.9]	0.13, <0.001 [-2.7/-2.2]	0.23, <0.001 [-3.4/-1.7]	0.08, 0.018 [-2.9/-2.3]
Baseline BMI SDS	0.10, <0.001 [-1.2/0.1]	0.01, 0.798 [-2.3/0.1]	0.12, 0.006 [-2.7/-1.1]	0.04, 0.234 [-0.4/0.8]
Baseline GH dose (mg/kg/wk)	0.21, <0.001 [0.20/0.30]	0.04, 0.173 [0.20/0.35]	0.10, 0.026 [0.22/0.30]	0.10, 0.005 [0.26/0.33]

[Patient characteristics by diagnosis group]

Conclusions: Age at dx & GH initiation did not significantly decline for any dx, but increased for GHD, likely driving increases over time in USA & WEU. Coupled with increases in BL Ht SDS for all dx gps & all but 1 region, it appears that more pts with less severe growth disorders are receiving GH, especially GHD pts, perhaps reflecting referral or socioeconomic changes.

P2-d2-832 GH and IGF Physiology and Treatment 5

Final height after long-term growth hormone (GH) treatment of short children with GH-deficiency, born small for gestational age (SGA) and Turner syndrome (TS)

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Background: GH treatment is effective in improving height of short children with GH-deficiency, SGA and TS in childhood.
Objective and hypotheses: The aim of the study was to evaluate effect of long-term GH treatment on final height (FH) of short children with GH-deficiency, SGA and TS, using traditional dose for each disease with same time of treatment.
Methods: Study included 212 children with GH-deficiency (138M/74F, age 8,1±2,7 yrs at start treatment, dose of GH 0.033 mg/kg/day, treatment duration 7,0±0,8 yrs), 46 short children with SGA (all patients without GHD, 31 M/15F, age 7,9±2,5 yrs at start treatment, dose of GH 0.06 mg/kg/day, treatment duration 7,0±0,6 yrs) and 63 girls with TS (age 7,8±2,3 yrs at start treatment, dose of GH 0.05 mg/kg/day, treatment duration 7,0±0,3 yrs). There were made evaluations of Prognosis height (PH)(calculated by Bayley-Pinneau), Target height (TH) (for boys: [father height(cm) + mother height(cm)] + 13/2, for girls: [father height(cm) + mother height(cm)] - 13/2), FH (was defined as a bone age over 16 yrs for boys and over 14 yrs for girls or the growth rate less than 2 cm/year), anthropometric measurements and bone age. All girls with TS began to receive sex steroids when their bone age reached 11 yrs.
Results:

mean±SD	GHD		SGA		Turner syndrome
	boys	girls	boys	girls	
PH (cm)	141,6±8,2	129,6±9,1	152,7±6,7	141,0±4,1	141,8±4,2
SDS PH	-3,7±1,2	-4,4±1,6	-3,3±0,8	-3,4±0,5	-3,4±0,6
TH (cm)	177,5±4,8	161,6±5,4	178,0±4,3	162,1±5,4	161,9±5,6
SDS TH	0,5±0,4	-0,2±0,6	0,5±0,3	0,1±0,6	-0,1±0,7
FH (cm)	174,7±5,5*	160,4±6,7*	171,7±4,7*	156,2±3,5*	148,8±4,0*
SDS FH	-0,2±0,6**	-0,4±0,7**	-0,9±0,6**	-0,7±0,5**	-2,2±0,6**
Δ FH-PH (cm)	33,1±3,1	30,8±3,2	18,4±2,7	15,2±2,4	7,0±2,1
Δ SDS FH-PH	3,9±0,5	3,7±0,4	2,5±0,3	2,7±0,3	1,2±0,2

[p< 0,001 vs. PH, ** p< 0,01 vs. SDS PH]*

Conclusions: Long-term GH treatment providing a good height gain significantly improved FH vs. PH in all study groups with the best result of patients with GHD and with the worst result of patients with TS.

P2-d2-833 GH and IGF Physiology and Treatment 5

The effect of gonadotropin-releasing hormone analog combined with anabolic steroid hormone and/or growth hormone on adult height in boys who enter puberty with short stature

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Background: Children who enter puberty at short grow up short as adults, since among the clinical factors before puberty the height at onset of puberty has the strongest correlation with adult height.
Objective and hypotheses: We studied whether GnRH analog (GnRHa) combined with anabolic steroid hormone and/or growth hormone can improve adult height in boys (treated group) who enter puberty below 135cm and compared with the adult heights in untreated 29 boys (untreated group) who enter puberty below 135cm.
Methods: Thirty boys who enter puberty below 135 cm were treated with GnRHa with GH and/or anabolic steroid hormone. Ten patients (Group A) were treated with GnRHa and GH, sixteen patients (Group B) with GnRHa and anabolis steroid hormone (AH), and four patient (Group C) with GH, GnRHa and AH. Mean age at onset of puberty was 11.2 years and 12.1 years ($p < 0.05$) in treated and untreated groups, respectively. Mean height at onset of puberty was 131.6 cm and 130.5 cm (not significant), respectively. Mean ages of start and stop of GnRHa were 12.3 years and 16.4 years, respectively, and mean duration of GnRHa treatment was 4.1 years.
Results: Mean pubertal height gain was significantly greater in GnRHa treatment group than untreated group (32.6 cm vs 26.3 cm) and mean adult height was significantly greater in GnRHa treatment group than untreated group (164.2 cm vs 156.8 cm). Among the treatment group, pubertal height gain tended to be greater in Group C, but there was no significant difference (Group A vs Bvs C: 31.4 cm, 62.8 cm, 34.7 cm). Since AH promotes pubertal maturation, addition of AH is psychologically acceptable for patients than addition of GH. Increased liver enzyme occurred in one patient as a side effect of AH.
Conclusions: In conclusion, GnRHa treatment combined with AH and/or GH was effective to increase pubertal height gain and to improve adult height in boys who enter puberty at short.

P2-d2-834 GH and IGF Physiology and Treatment 5

Adult height of girls with Turner syndrome treated from before six years of age with a fixed per kilo GH dose

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Objective: To evaluate adult height (AH) in 25 girls with Turner Syndrome (TS), who were treated from before 6 years of age for 10.0 ± 1.7 years with a GH dose of 0.33 mg/kg/week.
Methods: After a 6-month pretreatment follow-up all patients were 6-monthly measured under therapy to assess height (H) and H velocity (HV) until AH achievement.
Results: Following initial acceleration, HV significantly declined after the first 4 years of therapy. At the end of the 6th year of therapy H delta was 1.9 ± 1.1 SDS. Thereafter H delta decreased, attaining its nadir at AH achievement. Bone maturation velocity did not significantly change throughout the prepubertal period. According to Lyon standards for TS, mean AH (SDS) was significantly higher than pretreatment H ($p = 0.00006$), with a mean H delta of 0.9 ± 0.9 SDS. However, the prevalence of patients with pathological H (< -2 SDS according to Sempé standards) at the end of treatment was close to that recorded at therapy start (64% vs 72%). No significant differences in terms of

AH were found between patients with either X monosomy or X-chromosomal abnormalities and between girls with either spontaneous or induced puberty.
Conclusions: We infer that the therapeutic regimen adopted in this prospective study is sufficient to induce a significant growth acceleration during the first years, whereas it is not sufficient to prevent the subsequent waning effect after initial height delta.

P2-d2-835 GH and IGF Physiology and Treatment 5

Normalised pubertal growth and adult height in children with multiple pituitary hormone deficiency (MPHD), results from a randomised clinical trial

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Background: Gain in $height_{SDS}$ during puberty is rarely seen on current growth hormone (GH) treatment. Pubertal increase in GH secretion and both diurnal rhythm and slow increment in sex steroids are not considered.
Objective and hypotheses: Can more physiological therapy induce pubertal height gain and increase adult height (AH) in children with MPHD?
Methods: 21 children (14 boys**)** with MPHD and 2 girls with GH and gonadotrophin deficiency with >1 prepubertal year on 33 µg/kg/day, GH^{33}, were randomized to either 67 µg/kg/day, GH^{67}, given as one (n=7; 6 boys) or divided into two daily injections (n=8; 4 boys), or to stay on GH^{33} (n=6; 4 boys). Sex steroid replacement was 17ß estradiol patches (Estraderm®) or oral testosterone-undekanoat (Undestor®). Growth was assessed as gain in $height_{SDS}$ for prepubertal, pubertal and total period; AH was given vs population ($height_{SDS}$) and vs parents ($diffH\text{-}MPH_{SDS}$).
Results: There was a significant gain in $height_{SDS}$ during puberty for the total group (0.7 SDS, $p< 0.001$) for GH^{67} (0.9 SDS, $p< 0.01$ vs '0') and GH^{33} (0.3 SDS, ns within group and vs high dose). The total gain in $height_{SDS}$ was for 'all' 2.8 SDS and for GH^{67} 3.1 SDS ($p< 0.001$ for both); for GH^{33} 2.0 SDS ($p< 0.03$). In the GH^{67} groups 64%, and in GH^{33} 50%, reduced their GH dose due to subjective normalized stature. Mean AH for boys was 183.7 cm (range 178-191), for girls 165.5 cm (range 158-170), expressed in SDS for all 0.2±0.8. AH_{SDS} and $diffH\text{-}MPH_{SDS}$ were above -2 SDS for all. Undestor® gave normal masculinisation but tall adult heights, while Estraderm® gave estradiol serum levels high enough for growth plate fusion.
Conclusion: High GH dose was favourable for pubertal and total height gain. Pubertal growth is also highly dependant on sex steroid, both dosing route and tempo.

P2-d2-836 GH and IGF Physiology and Treatment 5

Vitamin D and growth hormone treatment

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Background: Living in Sweden which is in the northern part of the world, above 35° of latitude implies a major risk of vitamin D deficiency. Prepubertal children show a marked seasonal variation in growth parallel to hours of sunshine. Vitamin D shows a similar pattern with the highest levels during late summer. Growth hormone (GH) promotes longitudinal growth in short prepubertal children.
Objective and hypotheses: The aim was to study the influence of seasonal variation in vitamin D levels on pretreatment growth and first year growth response to GH treatment.
Methods: The study group consisted of 279 short prepubertal children, 223 boys age 9.08±2.6 SD, 56 girls age 7.79±1.65, belonging to registered clinical trials in Sweden. GH was given in the range 17-100 µg/kg/day, mean 0.42 µg/kg/day. 82 children were GHD (GHmaxAITT/24h profile ≤ 10 µg/L).
Vitamin D was measured in serum using ISYS 25-hydroxyvitamin D assay (IDS, UK). Statistics used were Students t-test and Tukey's HSD Post-hoc test.
Results: Seasonal variation was observed in vitamin D levels with lower levels during November-May (range 51-64 ng/ml), min April (51±15 ng/ml) and highest during June to October (range 67-96 ng/ml), max August (96±24, ng/ml).
Vitamin D levels decrease during first year of GH treatment from 66.40±19 ng/ml to 61.64±19.4 ng/ml (p=0.004). With a mean change of -5.03±15 ng/ml, corresponding to a 5.9±21% decrease, in vitamin D levels during first year of GH treatment.
No relations were seen between either pretreatment growth or first year growth response on GH treatment and vitamin D levels at start, at 1 year or the change. The degree of GH deficiency had no influence on the vitamin D levels. Furthermore no significant difference between boys and girls was found.
Conclusions: Even though a seasonal variation exist in both vitamin D levels and growth, no relation between pretreatment growth, first year growth response during GH treatment and vitamin D was found.

P2-d3-837 GH and IGF Physiology and Treatment 6

Effects of treatment with recombinant growth hormone in children with transient partial growth hormone deficiency

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Background: Treatment with recombinant growth hormone (rGH) remains questionable in patients with GH concentrations between 5 and 10 ng/ml, defined as partial GHD (pGHD).
Objective and hypotheses: The aim of the study was to assess the effects of rGH therapy in children with pGHD.
Population: Study group (SG) comprised 21 short-statured patients (12 boys) in the mean age 13.7±1.5 yrs and peak GH concentrations of 5-10 ng/ml in two stimulation tests, treated with rGH for 3.17±1.3 yrs. At the study completion their peak GH was >10 ng/ml. They were matched to 19 untreated children (12 boys) with idiopathic short stature (ISS) in the mean age of 13.2±1.5 yrs (Control group-CG). In the SG 16 (84.2%) children entered puberty (Tanner 2-3), whereas 11 (58%) ISS subjects were prepubertal. Height deficit (HSDS), deviation from the mid-parental height (HSDS-mpSDS) were assessed in all children at diagnosis and after reaching final height. Predicted height (PHSD) was calculated by Bayley-Pinneau method based on bone age delay.
Results: At the study entry there was no statistically significant difference between SG and CG with respect to bone age delay, mean height deficit with reference to population and parents (HSDS0 2.89±0.61 *vs* -2,83±0,41; p>0,05; HSDS-mpSDS0 -1.88±0.63 *vs* -1.73±0.68; p>0.05) or predicted final height (PHSDS -1,31±1,24 *vs* -1,60±1,00; p>0.05). Final height reached by children with pGHD was comparable to predicted height (HSDS fin -1.28±0.88) and did not differ from the height achieved by untreated ISS children (HSDSfin -1.57±0.92). In children with pGHD height gain was significantly better in subjects who started rGH therapy in prepubertal period.
Conclusions: Study results did not show beneficial effects of rGH treatment in children with pGHD as compared to untreated ISS subjects. Application of more stringent criteria for pGHD is probably necessary.

P2-d3-838 GH and IGF Physiology and Treatment 6

Comparison of IGF-1 secretion in children with short stature with respect to growth hormone secretion after falling asleep and in stimulating tests

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Background: Stimulating tests are the main tools for diagnosing growth hormone (GH) deficiency (GHD) in children with short stature. In Poland, the assessment of GH secretion after falling asleep has gained a significance of screening procedure. However, GHD has recently been defined as secondary IGF-I deficiency.
Objective and hypotheses: The aim of the study was to compare IGF-I and IGFBP-3 secretion in the patients with decreased or normal GH secretion after falling asleep (sleepGH) and in 2 stimulating tests (stimGH).
Methods: The analysis comprised 1000 children with short stature. In all the patients sleepGH and stimGH was assessed, together with basal of IGF-I and IGFBP-3 serum concentrations. The patients were divided into the following groups:
GHD-1 -both sleepGH and stimGH < 10.0 ng/ml;
GHD-2 - stimGH < 10 ng/ml, while sleepGH >10 ng/ml;
NSD (neurosecretory dysfunction) - stimGH >10 ng/ml but sleepGH < 10 ng/ml;
ISS (idiopathic short stature) - both sleepGH and stimGH >10 ng/ml.
The values of height SDS, IGF-I SDS for age and sex and IGF-I/IGFBP-3 molar ratio were compared among the groups.
Results: There was no difference in height SDS among all the groups of patients, while significant differences ($p< 0.05$) in IGF-I SDS were found among all the groups except for one between GHD-1 and GHD-2, while IGF-I/IGFBP-3 ratio was significantly lower ($p< 0.05$) in GHD-1 than in all other groups (see Table1).

Group	GHD-1	GHD-1	NSD	ISS
Number of patients	227	96	262	415
Height SDS	-2.83±0.88	-2.57±0.55	-2.76±0.70	-2.78±0.82
IGF-I SDS	-1.61±1.20	-1.45±1.04	-1.24±1.12	-0.92±1.08
IGF-I/IGFBP-3	0.19±0.08	0.23±0.10	0.22±0.11	0.25±0.12

[Table 1]

Conclusions: Decreased GH secretion in stimulating tests but not after falling asleep is associated with more severe IGF-I deficiency. The assessment of GH secretion after falling asleep seems to be not useful as a screening procedure in diagnosing GHD in children with short stature.

P2-d3-839 GH and IGF Physiology and Treatment 6

Contrasting factors that impact the response to growth hormone therapy (GHT) in children with idiopathic growth hormone deficiency (IGHD) and idiopathic short stature (ISS)

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Background: NordiNet® and NovoNet® are observational registries for patients treated with Norditropin® (somatropin) as prescribed by the physicians.
Objective and hypotheses: To assess if stimulated peak-GH, gender and average cumulative GH dose affect the 2-year change in height standard deviation score (ΔHSDS) in response to GHT in children with IGHD or ISS.
Methods: 3041 IGHD (peak-GH< 10 ng/ml with no known-causes of GHD) and 487 ISS (peak-GH≥10 ng/ml) children were included. ΔHSDS was analysed for pooled IGHD and ISS patients using a multiple regression analysis (MRA). The pre-pubertal (PP) cohort (based on Tanner stage or age) was analysed separately to minimize sex steroid effects on growth.
Results: At baseline, ISS *vs* IGHD patients had similar age (yr) (10.7 *vs* 10.6; P=0.23), higher peak-GH (18.8 *vs* 5.7; $P< 0.0001$), lower HSDS (-2.37 *vs* -2.17; $P< 0.0001$), and lower target HSDS (-0.82 *vs* -0.48; $P< 0.0001$). In PP cohort, ISS *vs* IGHD patients had older age (7.6 *vs* 7.1; P=0.01), higher peak-GH (18.1 *vs* 5.6; $P< 0.0001$), similar HSDS (-2.56 *vs* -2.59; P=0.70), and lower target HSDS (-0.92 *vs* -0.55; $P< 0.0001$). Average cumulative GH dose (μg/kg/d) was 46.2 for IGHD, 52.5 for ISS ($P< 0.0001$); 40.5 for PP-IGHD, 48.9 for PP-ISS ($P< 0.0001$). 2-y ΔHSDS was 0.99 for IGHD, 0.86 for ISS; 1.20 for PP-IGHD, 0.98 for PP-ISS. MRA showed that in PP cohort peak-GH had a significant negative influence on ΔHSDS (higher peak, lower ΔHSDS); Being female was also negatively correlated with ΔHSDS.
Conclusions: In this pooled analysis of two large registry datasets, IGHD patients had lower peak GH and GH dosage than ISS patients. The lower target HSDS in ISS patients likely reflects inclusion of some patients with familial short stature. MRA in PP cohort revealed a significant inverse correlation of peak-GH and female gender on 2-y ΔHSDS in the pooled IGHD/ISS population. The inverse correlation of peak GH is related to GH resistance in ISS and impact of gender remains to be elucidated.

P2-d3-840 GH and IGF Physiology and Treatment 6

A 4-year, open-label, multi-centre, randomised, 2-arm study of Genotropin® growth hormone in patients with idiopathic short stature: analysis of 4-year data comparing efficacy, glucose homeostasis, and IGF-I between an individualised, target-driven regimen and standard dosing

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Background: Idiopathic short stature (ISS) is an FDA-approved indication for growth hormone (GH) up to 0.47 mg/kg/wk.
Objective and hypotheses: Compare treatment efficacy, glucose homeostasis, and IGF-I over 4 yr between formula-based vs standard GH treatment of children with ISS (formula modified from Albertsson-Wikland et al*).
Methods: 4-yr, open-label, randomized (2:1) study of 316 children comparing individualized treatment (IT) of Genotropin® [0.18-0.7 mg/kg/wk for the first 2 yr then randomized again (1:1) to 0.18 or 0.24 mg/kg/wk] vs standard ISS treatment (ST) (0.37 mg/kg/wk). Height (Ht) was measured at screening and at 4-mo intervals for 4 yr. Efficacy variables were evaluated at 4 yr using treatment, age, and gender as model factors, and baseline Ht SDS as a covariate (ANCOVA).
Results: Subjects (89 F) were prepubertal, 3-14 yr, and GH-naïve. Bone age (BA) ranged 3-10 yr (M) and 3-9 yr (F), Ht SDS -3 to -2.25, Ht velocity < 25th percentile for BA, and peak GH ≥10 ng/mL(data shown in the Table). All groups had substantial Ht gain without safety concerns. After 4 yr, ΔHt, ΔBA, fasting glucose and insulin, and HbA1c were similar in all treatment groups. IGF-I was >1.1 times the upper limit of normal at least once for 25.1% of IT and 19.5% of ST subjects.

Mean(SD)	IT			ST		
Time(yr)	0	2	4	0	2	4
Subjects(n)	202	184	172	114	101	97
Ht SDS(SD)	-2.6 (0.4)	-1.4 (0.5)	-1.2 (0.7)	-2.5 (0.3)	-1.4 (0.5)	-1.1 (0.8)
Ht SDS gain(SD)		1.1 (0.5)	1.3 (0.7)		1.1 (0.4)	1.4 (0.7)
HbA1c %(SD)	5.0 (0.3)	5.3 (0.4)	5.2 (0.3)	5.0 (0.3)	5.4 (0.3)	5.3 (0.3)
IGF-I SDS(SD)	-0.6 (0.5)	0.5 (0.7)	0.4 (0.6)	-0.6 (0.4)	0.4 (0.6)	0.5 (0.7)

[Table]

Conclusions: All treatment arms demonstrated similar growth efficacy, glucose homeostasis, and comparable IGF-1 changes during 4 yr of GH.

P2-d3-841 GH and IGF Physiology and Treatment 6

Audit of patients who have ceased treatment in a national growth hormone (GH) program

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Background: In Australia GH treatment is subsidised for a range of diagnoses. Demographic, diagnostic, treatment and response data are recorded in the OZGROW database. Criteria are set for treatment completion or exclusion due to non-response.
Objective and hypotheses: To determine completion or non-response rates and provide a summary of the GH program. This abstract overview will not attempt to breakdown results by diagnosis or gender. **Hypothesis:** that GH treatment improves height (Ht) to a clinically relevant degree.
Methods: 4191 patients ceased treatment between 1988 and 2013. Commencement and cessation ages and Hts (SDS), treatment duration, and delta-Ht-SDS were measured. % reaching response cut-offs (10th adult centile:167.66cm(boys), 155.02cm(girls) or bone age (BA) of 15.5y:boys, 13.5y:girls) or excluded for non-response (Ht velocity < 4cm/y while on highest dose) were recorded.
Results: Mean starting Ht was -2.78 at 9.8y of age. Mean duration of treatment 5.02y. Final age 14.9y. Mean Ht at cessation -1.86S; equivalent to an increase of 156.8 to 163.5cm (+6.7cm) for boys or 145.2 to 151.2cm (+6.0cm) for girls. Mean delta-SDS was 0.94 or 0.20/y.
19.0% reached the 10th adult centile and 27.8% attained BA response cut-off. 40.4% attained either or both cut-offs. 8.1% of those not reaching a cut-off were classified as non-responders (4.9% of all). Thus, 54.7% of cessations not explained by these criteria. Ht-SDS, treatment duration, and final age were for those reaching a cut-off (-1.2, 5.9y, 16.2y), non-responders (-2.5, 5.9y, 15.0y), and unexplained (-2.3, 4.3y, 14.0y). 14.7% had attained mid-parental Ht SDS (18.2% within 0.2SDS). 52% of last Hts were recorded 1-6 months after cessation. Adult Hts were recorded in 5.5-7.6% depending on criteria used.
Conclusions: Clinically relevant height increases are seen with greatest gains in those reaching response cut-offs. Many cessations are unexplained and have a relatively poor response.

P2-d3-842 GH and IGF Physiology and Treatment 6

Paternally inherited deletion of 6q24.3 with Silver-Russell like syndrome phenotype and GH deficiency

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Background: Interstitial deletions of the long arm of chromosome 6 are relatively uncommon and to date only a few cases regarding congenital malformation syndromes associated with a paternal deletion of 6q24.3 have been reported.
Objective and hypothesis: We described a new patient with *de novo* paternal interstitial deletion of 6q24.3, associated with Silver-Russell like syndrome phenotype, and growth failure due to growth hormone (GH) deficiency.
Population and/or methods: We evaluated the auxological characteristics and we studied the growth hormone axis of a male with *de novo*, paternal, 6q24.3 interstitial deletion.
Results: The propositus was born at 35 weeks by elective cesarean performed because of IUGR: birthweight 1,900 gr (4th centile), length 45.0 cm (17th centile), head circumference 33 cm (4th centile).
Early psychomotor development was mildly delayed. He showed hypoplastic left colon, bilateral inguinal hernia, dysplastic tricuspid and pulmonary valves, recurrent otitis media, poor feeding, gastro-esophageal reflux, bilateral pseudopapilledema and astigmatism.
He had important growth failure with relative macrocrania: at 3.75 years, height was 88.2 cm (< 3° centile), weight 11.500 Kg (3° centile). Target height was on 50th centile. Bone age was delayed (1.5 years to 3.66 years of chronological age). His IGF-I concentration was low-normal (78 ng/ml), while growth hormone stimulation tests showed a low response after clonidine (GH peak 4.46 µg/l), and arginine (GH peak 3.14 µg/l). MRI unrevealed pituitary gland hypoplasia**.** SNP (Single Nucleotide Polymorphysm)-array showed a 6q24.3 interstitial deletion. Microsatellites study demonstrated that the deletion occurred in the paternal chromosome 6 .
Conclusion: We confirm that a recognizable congenital malformation syndrome is associated with a 6q24.3 deletion of paternal origin. We also suggest to evaluated growth hormone axis in children with 6q24.3 deletion and growth failure.

P2-d3-843 GH and IGF Physiology and Treatment 6

Growth response (year 1 delta height SDS) and percentage of poor responders in GH-treated patients are functions of the position of the diagnosis in the continuum of short stature disorders

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Background: Growth response is increasingly examined for clinical benefit and to justify GH prescribing.
Objective and hypotheses: Assess:
1) year 1 delta height (Ht) SDS,
2) poor responders (%) related to the continuum of GH-IGF-1 axis defects.
Methods: 'Poor year 1 response' = delta Ht SDS < 0.5. 502 GH-naïve subjects, mean (SD) age 9.43 (3.58) yr, males, pre- /early pubertal (TV ≤6ml) (n= 373), females Br Stage 1 (n=129), initiating GH (NutropinAq®) participated in a post-marketing surveillance study (iNCGS, Ipsen Pharma). Mean (SD) baseline Ht SDS: -2.37 (0.82). Peak stimulated GH defined the position in the continuum with allocation (Groups A to C): 434 GHD subjects, idiopathic (n=417), organic (n=17) had peak GH (ng/ml): < 3 (n=89, Group A), 3-5 (n=92, Group B). 5-10 (n=253, Group C). 68 subjects had peak GH >10 (Group D).
Results:

Group	A	B	C	D
Peak GH (ng/mL)	< 3	3-5	5-10	>10
Delta Ht SDS Mean (SD)	0.72 (0.61)	0.60 (0.42)	0.52 (0.76)	0.44 (0.48)
Poor responders (%)	37.2	44.9	51.2	62.1
Dose of GH (mg/kg/day)	0.030	0.029	0.028	0.030
Mean (SD)	(0.006)	(0.006)	(0.007)	(0.009)

[Delta Ht SDS, poor responders (%), GH dose]

Delta Ht SDS decreased and poor responders (%) increased with increasing peak GH, in line with expectations. Delta Ht SDS (n=485), adjusted for baseline, associated with peak GH ($p< 0.0001$). Delta Ht SDS differed ($\alpha=0.05$) in Groups A to C and A to D (mean difference [95 % CI]: 0.197 [0.063; 0.331] and 0.279 [0.104; 0.453]). Poor responders (%) differed between Groups A and C ($p=0.026$), A and D ($p=0.0026$). GH dosage did not differ between groups (at $\alpha=0.05$ level).
Conclusions:
1) Year 1 growth response and poor responders (%) are functions of the position in the continuum,
2) The continuum model can help to choose the optimal GH starting dose.

P2-d3-844 GH and IGF Physiology and Treatment 6

Increased growth rate response to rhGH treatment in a patient with a novel homozygous *IGFALS* mutation

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Introduction: Homozygous or compound heterozygous *IGFALS* mutations cause postnatal growth deficit associated with severely decreased IGF-I and IGFBP-3 levels that remain low after rhGH treatment.
Case study: We present the case of a 3yr old girl consulting for postnatal proportional growth deficit (-3.38 SDS), born to consanguineous parents at 39w; BW 2900 gr (-1.2 SDS), BL 48 cm (-1.4 SDS) and HC 34cm (-0.34 SDS). Her main auxological characteristics are summarized in the enclosed table.

rhGH treatment (mg/kg/d)	Chron. age (yrs months)	Height (cm) (SDS)	Bone age (yrs months)	IGF-I (ng/ml) (SDS)	IGFBP-3 (µg/ml)	Growth rate (cm/yr) (SDS)
-	3y 2m	84.5 (-3.38)	2y 6m	<25	-	-
-	5y	93.5 (-3.69)	3y 9m	<25	-	4.5 (-2.56)
0.04	5y 2m	94.5 (-3.7)	-	<25	-	6.2 (-0.34)
0.04	6y 2m	101.9 (-3.26)	4y 6m	<25	-	7.4 (+1.48)
0.04	7y 5m	108.8 (-3.23)	-	53 (-2.18)	-	5.9 (+0.57)
-	8	110.7 (-3.37)	-	34 (-3.73)	<0.5	2.85 (-3.0)
-	8y 11m	115.2 (-3.18)	-	29 (-4.54)	<0.5	4.9 (-0.42)
-	9y 11m	120.3 (-2.85)	9y 6m	<25	<0.5	5.1 (-0.42)
-	10y 11m	125.5 (-2.96)	11y	-	-	5.2 (-1.18)

[Proband's auxological data]

Hormonal tests at diagnosis revealed undetectable IGF-I as well as peak GH values of 2.96 ng/ml (clonidine), 27.5 ng/ml (L-Dopa/carbidopa) and 7.7 ng/ml (glucagon). At 5yr 2m she started treatment with rhGH (0.04mg/kg/d), leading to a significant increase in growth rate, despite persistant low IGF-I (s. Table). After 26 months, rhGH treatment was discontinued at the family's request, resulting in a dramatic drop in growth rate.
Molecular studies: GHR and *IGFALS* mutation screening by HRM and DNA sequencing detected a novel homozygous missense mutation, c.682A>G, p.Asn228Asp, in *IGFALS* exon 2. Both parents were heterozygous carriers. p.Asn228Asp affects a highly conserved residue located in the Leu rich domain (LxxLxLxxN/CxL) and results in undetectable ALS levels in the proband.
Conclusions: In our patient, rhGH significantly increased growth rate during the treatment window, despite of low IGF-I, suggesting that some patients with homozygous *IGFALS* mutations may benefit from rhGH therapy.

P2-d3-845 GH and IGF Physiology and Treatment 6

Bone structure change in childhood-onset GH deficient adolescents after cessation of GH treatment is mild and does not indicate the severity of GHD

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Background: The anabolic action of GH is suspected to be necessary for development of normal bone structure and stability in childhood and adolescence.
Objective: We aimed to study the changes in bone structure, density and strength in adolescents with childhood-onset GHD after stop of GH treatment.
Patients and methods: We studied 44 patients (12 females) at a mean (SD) age of 16.2 (1.6) yrs that had reached a near final height of -0.70 SDS (1.02). Age at start of GH treatment had been 7.25 (3.28) yrs, height SDS -3.10 (0.61) and stimulated GH peak 5.6 (2.0) ng/ml.
After 3 months off GH, 6 patients were classified to have severe GHD (sGHD) of adolescence according to an arginine-GHRH retest peak < 15 ng/ml and an IGF-I < 156 ng/ml. Six patients showed inconsistent (inGHD) and 32 normal endocrine results (nGHD).
Bone structure (cortical area = CA), density (cortical = CD) and strength strain index (SSI) were measured with pQCT (XCT 2000, Stratec Inc.) on the non-dominant radius (65% measure-point) at stop (0) of GH treatment and 6 months later (6).
Results: The changes of bone parameters during 6 months off GH were of small degree and did not show any correlation with the GH peak or IGF-I at retesting ($R< 0.1$, $p>0.1$). In addition, changes of the bone parameters were similar in all 3 subgroups. See table (mean (SD)).

	sGHD 0	sGHD 6	nGHD 0	nGHD 6	inGHD 0	inGHD 6
CD (mg/cm³)	1067 (46)	1101 (35)	1058 (50)	1087 (41)	1089 (14)	1097 (29)
CA (mm²)	71 (22)	80 (23)	73 (16)	77 (16)	81 (8)	83 (4)
SSI (mm³)	281 (115)	305 (105)	274 (35)	290 (87)	275 (35)	303 (29)

[Results]

Conclusions: Bone structure change in childhood-onset GH deficient adolescents after cessation of GH treatment for 6 months is mild and does not indicate the severity of GHD. Long-term evaluation may be necessary to observe metabolic consequences of severe GHD in adolescence.

P2-d3-846 GH and IGF Physiology and Treatment 6

SOX3 duplication and growth hormone deficiency: a case with long-term follow-up

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Background: *SOX3* gene is located on the X-chromosome and both under- and overdosages of the gene lead to hypopituitarism. There are rare cases described and poorly reported with a long-term follow-up.
Objective and hypothesis: To study the auxological characteristics of a male with growth failure showing growth hormone (GH) deficiency and duplication of *SOX 3* (OMIM 313430*)*.
Population and/or methods: A male patients with short stature and GH deficiency, ocular dyspraxia and mental retardation, possibly due to *SOX3* duplication.
Results: Target height was normal (0.5 SDS). The patient was born at term with Caesarean delivery for podalic presentation: birth-weight (0.1 SDS), length (0.4 SDS), and head circumference (-0.3 SDS) were normal. The child showed neuromotor delay and ocular motor dyspraxia. At 3 years 11 months old the child carried out an endocrinological evaluation, for the important growth failure (height -2.4 SDS), showing a low IGF-I concentration (58 µg/L); thyroid hormone level was normal and celiac disease markers were negative. Bone age resulted considerably delayed. Growth hormone stimulation test discovered a classic GHD. MRI discovered a pituitary hypoplasia with ectopic neurohypophysis.
The auxological follow-up showed a very good response to rhGH treatment and at 9 years old the height was 0.3 SDS, weight 0.1 SDS, and the pubertal evaluation was PH1 AH1 T2 ml bilaterally. For the presence of intellectual disability and MRI abnormalities (hypoplastic anterior and ectopic poterior pituitary gland) clinical genetic evaluation was carried out and. CMA (Chromosomal Micro Array) requested. Array-CGH (Comparative Genomic Hybridization) unrevealed a 7,8 Mb duplication in the region 26.3-27.3 of the long arm of chromosome X (dup Xq26.3-27.3) The duplicated segment contains *SOX 3* gene.
Conclusions: *SOX3* involvement should be considered in a male with short stature due to GH deficiency associated with mental retardation.

P2-d3-847 GH and IGF Physiology and Treatment 6

Long-term auxological and endocrinological evaluation of patients with 9p trisomy: a focus on growth hormone-insulin-like growth factor-I axis

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Background: Trisomy 9p is characterized by mental retardation, head and facial abnormalities, congenital heart defects, kidney abnormalities, and skeletal malformations. Affected children may also show growth and puberty retardation and delayed bone age.
Objective and hypothesis: To study the auxological and endocrinological characteristics of 9p trisomy patients.
Population and/or methods: We describe three girls and one boy with 9p trisomy showing important growth failure.
Results: The target height was normal in all families, ranging from 0.1 SDS and -1.2 SDS. The patients showed a low birth-weight (from -1.2 to -2.4 SDS), birth length (from -1.1 to -3.2 SDS), and head circumference (from -0.5 to -1.6 SDS). All patients presented an important growth retardation at 9p trisomy diagnosis for height (from -3.0 to -3.8 SDS), whereas BMI ranged from 0.0 to -0.9 SDS. Bone age, valued by Greulich and Pyle's method, resulted always considerably delayed. Growth hormone stimulation test evaluation discovered a classic GHD in patient 1, 3, and 4. On the contrary, patient 2 discovered a GHNSD. Plasmatic concentrations of IGF-I and IGFBP-3 were low in all patients (from -2.0 to -3.4 SDS, and from -1.9 to -2.8 SDS, respectively). The auxological follow-up showed that all rhGH treated patients discovered a good response to GH therapy, whereas patient 3 and 4, not treated for family's decision, not experienced a significative catch-up growth. The pubertal onset was always delayed, except in the patient 1, possibly related to different age of start of rhGH treatment.
The final height was in according to her target height in the patients that started rhGH treatment; patient 3 showed a final height very lower than their target height. The degree of height response and recovery appeared to be according to the earlier age of start of rhGH treatment.
Conclusions: An impaired growth hormone-insulin-like growth factor-I axis are common in patients with 9p trisomy syndrome.

P2-d3-848 GH and IGF Physiology and Treatment 6

The influence of growth hormone therapy on carbohydrate and lipid metabolism in children with growth hormone deficiency

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Background: It is well known that growth hormone increases blood glucose levels and decreases serum cholesterol by activating lypolysis.
Objective and hypotheses: To analyze the effect of the recombinant human growth hormone (rhGH) treatment on carbohydrates and lipid metabolism in children with growth hormone deficiency (GHD).
Methods: We evaluated 45 children (16 girls, 29 boys) with GHD, mean age 10, 57 +/- 3, 59 yrs- (range 3 to 15 y), followed-up during GH therapy (0,025-0,035 mg/kg/day) for 4 years. Laboratory investigations included fasting glucose level and oral glucose tolerance test, serum insulin, total cholesterol, HDL and LDL cholesterol, triglycerides.
Results: Before treatment, fasting glucose levels and OGTT had normal levels, excepting one case with severe recurrent hypoglycemia. After one year of rhGH treatment, fasting glucose and insulin levels remained between normal ranges but OGTT revealed impaired glucose tolerance (IGT) and also, increased levels of serum insulin after OGTT in 5 cases (11,1%). For all 5 patients with IGT we initiated diabetic type meal planning. After the 2nd year of therapy, both IGT and serum insulin normalized and remained normal in the next 2 years of treatment. In one case, male, who stopped rhGH therapy at completion of growth, type 1 diabetes mellitus (DM) occurred, one year after ceasing rhGH therapy. No positive family history for diabetes was noted. Hyperlipidemia and hypercholesterolemia with increased HDLc were present at diagnosis in 6 cases (13,3%) and normalized after the first year of rhGH treatment.
Conclusions:
1. In children with GHD, rhGH treatment induces alterations of the the glucose tolerance which may be controlled with a correct diet; diabetes mellitus occurs only in genetically predisposed patients.
2. rhGH therapy has a positive effect on lipid metabolism, increasing lypolysis and decreasing serum total cholesterol and HDLc.

P2-d1-849 Glucose Metabolism 6

GCK gene mutations are a common cause of childhood-onset MODY maturity-onset diabetes of the young in a Turkish cohort

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Background: Heterozygous mutations in the glucokinase (*GCK*) gene cause mild fasting hyperglycemia (GCK MODY) and over 600 *GCK* mutations have been described. *GCK* mutations are one of the most frequent causes of

MODY in the world.
Objective: Here we aim to identify the frequency of GCK mutations in a Turkish pediatric population.
Method: From a cohort of 48 (25F/23M, aged 0.4-15.8 years) unrelated index probands suspected to have MODY, 20 were selected for *GCK* sequencing. These were selected according to HbA1c levels (≤ %7.5), fasting blood glucose (FBG) levels (100-145 mg/dl) and MODY calculator scores (≥%75).
Results: Eleven heterozygous mutations (4F/7M, aged 0.4-15.8 years) were identified, of which three are splicing mutations (c.46-2A>G, c.208+3A>T, c.1254-1G>C) and eight are missense mutations (p.L58P *novel*, p.F123S, p.F419C, p.G246A, p.K169R, p.R191Q, p.S151C, p.V367M). The patients' mean HbA1c level was 6,3±0,3 (5,9 - 6,7%) and mean FBG level was 118,4±8,6 (107-136 mg/dl). One of the 11 patients is treated with insulin. The low dose of insulin (0.27U/kg/day) and absence of anti-GAD autoantibodies suggests that type 1 diabetes is unlikely.
Conclusion: *GCK* mutations account for 23% of this pediatric cohort of patients with a suspected diagnosis of MODY. These patients are at low risk of developing diabetic complications and do not require pharmacological therapy. Further studies are in progress to define the etiology of diabetes in the remainder of the cohort.

P2-d1-850 Glucose Metabolism 6

Long-term endocrine and exocrine outcome of medically unresponsive diffuse congenital hyperinsulinism managed with near-total pancreatectomy: 18-years experience

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Background: Diffuse congenital hyperinsulinism (CHI) is a major cause of severe hypoglycaemia. One treatment option is near-total pancreatectomy, which carries a risk of diabetes mellitus (DM) and pancreatic exocrine insufficiency.
Objective and hypotheses: We report our centre's experience on 36 medically unresponsive diffuse CHI children managed with near-total pancreatectomy.
Methods: Following pancreatectomy, these children periodically underwent regular 24-hours blood glucose profile, controlled fasting studies and oral glucose tolerance tests. Clinical and biochemical evidence (faecal elastase 1) of pancreatic exocrine insufficiency was also evaluated.
Results: From 1994 to 2012, 36 children underwent near-total pancreatectomy for medically unresponsive diffuse CHI (Table 1; *Mean±S.D. #Median(Range)).

Patients (n)	Boys/ Girls (n)	Birth weight (g)*	Gestational age (wks)*	Age of presentation (days)#	Serum glucose (mmol/L)/ Serum Insulin (mU/L)*	Age at surgery (years)#
36	16/20	4080±730	38±2	1(1-14)	2±1/34±45	0.17 (0.08-10)
ABCC8/KCNJ11 analysis (n)						
Homozygous	Compound heterozygous		Dominant heterozygous		Contiguous gene deletion (Usher's syndrome)	
9	12		9		1	

[Table 1: Characteristics of 36 children]

Diffuse disease was diagnosed either by pancreatic venous sampling or ^{18}F DOPA PET-CT. Histology confirmed diffuse disease. Hypoglycaemia persisted in 16 (44%), necessitating total-pancreatectomy, octreotide, diazoxide and/or frequent high carbohydrate feeds. Over 8(± 4.75) years, 18 children developed DM. The cumulative risk of DM after 5 and 10 years post-pancreatectomy was 74% and 86% respectively. Twenty-six patients showed biochemical evidence of pancreatic exocrine insufficiency, only 17 (65%) of which developed clinical pancreatic exocrine insufficiency necessitating pancreatic enzyme replacement.
Conclusions: Near-total pancreatectomy for CHI is associated with high risk of DM, however not all patients with post-pancreatectomy develop clinical or biochemical pancreatic exocrine insufficiency. There seems to be a poor correlation between the levels of faecal elastase and clinical evidence of stool fat malabsorption.

P2-d1-851 Glucose Metabolism 6

Glucose response curve shape and diabetes risk in a cystic fibrosis population

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Background: Recently, the shape of glucose response at oral glucose tolerance test (OGTT) was suggested to be an early marker of type 2 diabetes risk among adults and latino-adolescents, respectively. The usefulness of this indicator has not been tested in cystic fibrosis (CF) population.
Objective and hypotheses: To investigate whether the 2h-OGTT glucose response curve shape is related with the prospective development of diabetes in CF population.
Methods: A cohort of 54 patients with CF (61% males) underwent OGTTs at clinically stable state of the disease. A total number of 178 OGTTs were performed along a 3 years follow-up. Based on the glucose response curve, patients were categorized as: monophasic (gradual rise concentration followed by a subsequent decrease), biphasic (initial rise followed by fall with a second rise, both >4.5 mg/dl) or indeterminate (gradual increase without a fall) phenotypes. OGTT glucose responses were classified as: normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or CF related diabetes (CFRD) (ADA 2013). We also analyzed insulin secretion (insulinogenic-index, HOMA-ß), insulin sensitivity (Matsuda-index, HOMA-IR) and ß-cell function (disposition-index). Statistical analysis: SPSS-program, non parametric test; data expressed in percentage, median and range (percentile 25-75), statistical significance $p < 0.05$.
Results: Median age at first OGGT 15.5 years (9.9-22.5). At first test 50% patients had NGT and none CFRD. During follow-up: 29% NGT, 46% IGT and 25% CFRD [n=13, median age 14.4 years (13.0-30.0)]. One year before diagnosis of CFRD all patients had monophasic-glucose-curve. Biphasic curves were present in 22% NGT patients, 5% IGT and none with CFRD. Indeterminate curves were found in 1% NGT patients, 7% IGT and 21% with CFRD. TABLE1.
Conclusions: Glucose response patterns at OGGT may represent an early marker of diabetes risk in CF population.

P2-d1-852 Glucose Metabolism 6

A novel ABCC8 misssense mutation in two siblings with variable expression of neonatal hyperinsulinism

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Introduction: Congenital hyperinsulinism possesses considerable clinical heterogeneity attributed partly to its diverse genetic causes. We present two siblings with persistent hyperinsulinemic hypoglycemia and a newly discovered ABCC8 missense mutation.
Case study: The boy was a third-born full-term child of a 29-years-old mother. He had birth-weight of 4660 g, retarded cardiopulmonary adaptation and perinatal asphyxia. Hypoglycaemic episodes without seizures appeared right after birth. Fasting insulin of 30.19 mIU/ml was recorded at BGL of 1.8 mmol/l. At physical examination the patient did not display features of syndromic hyperinsulinism. At 10 postnatal days he was discharged from the maternity with BGL>3.0 mmol/l and no further investigations were performed. The patient was referred to us at 2 months of age due to hypotonia and registered hypoglycemia. He showed mild axial hypotonia and unilateral congeni-

tal leukocoria. Laboratory investigations showed persistent hypoglycemia with BGL between 1.5 and 2.9 mmol/l and insulin levels of 6.91 and 6.52 mIU/ml. All other laboratory and imaging tests, including brain MRI, were normal. We initiated treatment with i.v. dextrose and Diazoxide up to 12 mg/kg/day. The hypoglycaemic episodes abated. The first-born 5-years-old sister was large for gestational age and experienced early postnatal severe hypoglycemic episodes, generalized seizures and severe brain damage with leukomalacia. A genetic testing with sequence analysis of the *ABCC8, KCNJ11and HNF4A* genes was performed. It showed that both children were compound heterozygotes for the ABCC8 missense mutations: the novel c179T>A inherited from the unaffected mother and c4664G>T mutation inherited from the unaffected father, identified previously in unrelated patients.
Conclusion: This new likely pathogenic missense mutation in the ABCC8 gene warrants further studies mostly because of the variable clinical presentation.

P2-d1-853 Glucose Metabolism 6

Glycaemic control and concomitant autoimmune diseases in paediatric type 1 diabetes patients

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Background: Patients with Type 1 Diabetes (T1D) have concomitant autoimmune diseases more frequently than the general population, indicating genetic predisposition to develop autoimmune phenomena. However, it is not yet established whether the presence of others autoimmune diseases may be an indicator of worse metabolic control and prognosis in patients with T1D.
Objective and hypotheses: To investigate if presence of concomitant autoimmune diseases may influence glycemic control and prevalence of acute and chronic complications of diabetes in children and adolescents with T1D.
Methods: Cross-sectional study of 247 children and adolescents with T1D controlled at a single reference Pediatric Diabetes Unit. In patients with and without concomitant autoimmune diseases: mean HbA1c levels [HPLC Menarini™ (normal value: 5.3±0.4%)], number of ketoacidosis and severe hypoglycemia episodes and the prevalence of chronic complications. Statistical analysis: SPSS™ 17.0.
Results: Mean age of the cohort: 12.6 ± 4.6 (47% female). Mean age at T1D onset and T1D duration 6.1±4.3 and 6.4±4.3 years, respectively. 72%/28% were treated with MDI and CSII, respectively. Mean HbA1c levels 6.9 ± 0.69%. 15% of T1D patients present an additional autoimmune disease: celiac disease: 8%; thyroid autoimmune disease: 5% (83% chronic lymphocytic thyroiditis, 17% Graves' disease), hepatitis (1 patient); Schonlein-Henoch purpura (1), chronic gastritis (1), autoimmune growth hormone deficiency (1). Chronic complications of diabetes were not present in any patient. Table 1.

Patients	Total n = 247	Concomitant autoimmune disease. n = 36 (15 %)	No other autoimmune disease n = 211 (85%)	p
HbA1c	6.9±0.69%	6.8±0.58%	6.9±0.71%	0.41
Ketoacidosis*	4.5	5.5	4.2	0.83
Severe hypoglycaemia*	2	2	0	-

[Table 1]
* episodes/100 patients/past year

Conclusions: The presence of other autoimmune diseases does not worsen glycemic control neither increases the prevalence of diabetic complications in children and adolescents with T1D.

P2-d1-854 Glucose Metabolism 6

Catch-up growth pattern as early predictor of deranged insulin sensitivity in term SGA children at 12-18 months

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Background: 2.3-10% of infants are born SGA. Most achieve catch-up growth (CUG) by 2 years, 15% continue to experience poor growth. Tempo of postnatal weight gain carries elevated risk of metabolic disease later in life. But literature at early age is scarce.
Objective: Estimate insulin levels in term SGA babies as early as 12-18 months and association with CUG.
Methods: Birth and current weight and length of fifty term SGA (< 10thpercentile) children at 12-18 months was recorded. Data analyzed for CUG (gain in weight/ length SDS or both of >0.67). Fasting and post glucose load samples taken to measure glucose and insulin levels. Insulin sensitivity evaluated using homeostatic model assessment index (HOMA-IR).
Results: 30 (60%) showed CUG, 18 (36%) & 25 (50%) displayed catch up growth in weight (WCUG) & length (LCUG). Fasting insulin higher in CUG (5.8±7.6uIU/ml) vs NCUG (2.8±1.9uIU/ml), p= 0.06; but post load insulin significantly higher among all with CUG (9.7±10.7) vs NCUG (4.3±3.4), p= 0.04. WCUG (7.3±9.2) had significantly higher fasting insulin (vs NWCUG 3.0±2.5, p= 0.01) when compared to LCUG (5.9±8.3) vs NLCUG 3.2±2.2, p=0.2. Glucose levels were similar. HOMA-IR value significantly higher in CUG (1.34, p=0.02) and WCUG (1.76, p=0.002) infants, difference being insignificant when stratified according to length (1.3, p=0.2), suggesting rapid gain in weight, not length determines higher HOMA value (correlation r=0.335, p=0.01) and susceptibility to decreasing insulin sensitivity. No correlation between change in length SDS and HOMA (r=0.07, p=0.6) was observed.
Conclusions: Early postnatal growth before 2 years is critical for identification of deranged insulin sensitivity. Hyperinsulinemia was observed amongst SGA babies showing weight catch up by as early as 12 months of age, which may be an early predictor of 'insulin resistance'- the cornerstone of adult metabolic syndrome.

P2-d1-855 Glucose Metabolism 6

Impact of glycaemic control on LDL cholesterol (LDL) in type 1 diabetes (T1D) from childhood to young adulthood

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Background: Uncontrolled diabetes and hyperlipidemia influence cardiovascular risk. Improving glycemic control (A1c) is often an initial strategy to reduce LDL levels in youth with T1D.
Objective and hypotheses: To describe trajectories of LDL levels and the impact of improvements in A1c on LDL levels from childhood to adulthood in youth with T1D under routine care.
Methods: We assembled longitudinal data related to A1c and LDL levels from 265 youth with T1D. All were ≥8 years and < 16 years old at baseline and ≥20 years by end of observation; median follow-up was 10.7 years (range 4.3-15.6). There was a mean of 8.4±3.7 LDLs/patient with a mean interval of 1.7±0.8 years between LDL levels. Longitudinal multivariate analyses (mixed models) described the impact of A1c on LDL over time adjusting for age, T1D duration, sex, weight status, and initial LDL. Analyses assessed the relationship between an absolute decrease in A1c of ≥1% and either an absolute decrease in LDL values or achievement of an LDL threshold < 100 mg/dL.
Results: In youth (42% male), aged 13.1±1.9 years with T1D duration 6.1±3.2 years at baseline, mean A1c was 8.6±1.3% and LDL was 93±28 mg/dL. At last observation, mean age was 24.0±2.6 years, A1c was 8.7±1.6%, and LDL was 98±34 mg/dL. Half the youth (n=129, 49%) had 1 or more LDL levels ≥100 mg/dL during childhood. Most (103/129, 80%) continued to have LDL ≥100 mg/dL into adulthood.
Longitudinal multivariate analysis yielded an LDL decrement of 4.5±8.1 mg/

dL per 1% decrease in A1c (p< .0001). In the 97 youth with childhood LDL levels ≥100 mg/dL and an improvement in A1c of ≥1% during follow-up, 48% achieved LDL < 100 mg/dL; mean A1c reduction of 2.2±1.1% was related to an LDL decrement of 15.4±24.5 mg/dL.
Conclusions: Dyslipidemia in youth with T1D often persists into early adulthood. Glycemic control impacts LDL levels but lowering A1c ≥1% is often inadequate to achieve LDL levels < 100 mg/dL.

P2-d1-856 Glucose Metabolism 6

The relationship between glucose variability and oxidative stress in children with type 1 diabetes

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Background: A strong relationship between glucose variability and oxidative stress in type 2 diabetes on oral medication has been reported.
Objective and hypotheses: The purpose of this study is to reexamine the relation between glucose variability and oxidative stress in T1DM children.
Methods: Case-control study of 70 T1DM children on CSII treatment underwent CGMS. During the measurement, patients collected 24 h urine samples for determination of urinary excretion rates of 8-iso-prostaglandin F2α (8-iso-PGF2α) to estimate oxidative stress. Standard deviation (SD) and mean amplitude of glycemic excursions (MAGE) were calculated as markers of glucose variability. Postprandial contribution to glycemic instability was assessed by determining the mean postprandial incremental area under the curve (IAUC) and mean postprandial glucose excursion (MPPGE). Compared with the data of 20 age- and sex-matched healthy controls. The correlation between glucose parameters and index of oxidative stress were analyzed.
Results: Median urinary 8-iso-PGF2α excretion rates was higher in patients than healthy controls: 360.9 (275.7-374.1) pg/mg creatinine vs 115.5 (62.3-140.7) pg/mg creatinine (p< 0.01). Spearman correlation showed significant relations for SD (r=0.26, p=0.006), MAGE (r=0.25, p=0.018), IAUC (r=0.4, p< 0.01) and MPPGE (r=0.35, p=0.001) with urinary 8-iso-PGF2α excretion rates.
Relationships between 8-iso-PGF2α excretion rates and either glucose parameters did not remain significant after adjustment for the other markers of diabetic control in multiple linear regression analysis (R^2=0.015, p=0.89).
Conclusions: We confirm that T1DM children have higher levels of urinary 8-iso-PGF2α excretion rates and glucose variability than healthy controls. But we did not find a relevant relationship between glucose variability and urinary 8-iso-PGF2α excretion rates, suggesting that in addition to glucose variability, other factors favouring oxidative stress may exist.

P2-d1-857 Glucose Metabolism 6

Next-generation sequencing (NGS) to identify a novel INS gene mutation in a family with maturity onset diabetes of the young (MODY)

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Background: Maturity Onset Diabetes of the Young (MODY) is a group of disorders that affect between 1-2 percent of all people with diabetes. The term MODY is used to describe a heterogeneous group of disorders caused by mutations in one of 13 known genes important to beta cell development, function, regulation, glucose sensing and the insulin gene itself. Up to 70% of referrals for genetic testing fail to identify a mutation, often due to the expense of testing multiple genes.
Objective: Using targeted next generation sequencing to identify mutations in known MODY genes
Methods: The proband is an 11yo girl, who presented in mild diabetic ketoacidosis. Over the following 12 months, she remained (GAD and IA2) antibody negative, with a low but measurable C-peptide and low insulin requirement of < 0.5units/kg/day, maintaining an HbA1c 5.7 - 6.3%. Her 8yo brother was subsequently diagnosed with diabetes, and her mother was diagnosed with diabetes at age 11 years. Of 15 members in her pedigree, 7 were affected with diabetes, spanning 4 generations.
Conventional Sanger sequencing was performed for MODY1 (*HNF4A*) and MODY3 (*HNF1A*), which was negative. Subsequently NGS was carried out on an Illumina Miseq using a Truseq Custom Amplicon panel. The panel contained six genes: *HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B* and *INS* (MODY1-5 and MODY 10)
Results: A novel heterozygous c.277G>A (p.Glu93Lys) mutation was detected in the Insulin gene (MODY 10). The mutation is located in one of the alpha helices and would be expected to affect binding to the insulin receptor.
Conclusion: Next generation sequencing may prove to be an accurate and efficient method of genotyping for monogenic conditions with multiple potential causes. Analysis of further family members and functional studies will be undertaken to confirm the pathogenicity of the mutation in this family.

P2-d1-858 Glucose Metabolism 6

BMI changes after diagnosis of type 1 diabetes mellitus in children and adolescents

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Background: Studies suggest that children and adolescents with type 1 diabetes (T1DM) have a higher prevalence of overweight than healthy children but the cause-effect relationship remains unclear, whether beta-cell stress induced by overweight contributes to the development of diabetes, or whether insulin treatment causes weight gain.
Objective and hypotheses: To study body mass index standard deviation score (BMI-SDS) before, at and after diagnosis of T1DM, and to identify factors associated with weight gain.
Methods: Studied retrospectively were 209 children and adolescents with T1DM treated at a tertiary care center. Retrieved from the patients' files were background, clinical, and laboratory data at diagnosis (at mean age 4.3±9.2 years) and during 6 years of follow-up. Anthropometric parameters of patients were compared along follow-up and with those of their parents and siblings.
Results: Mean BMI-SDS which was below average at diagnosis (-0.66±1.27), increased in the first 3 months to 0.37 ± 0.93, decreased between 3 to 6 months to 0.21±0.95 (p < 0.001), and remained stable between 6 and 12 months. Between 1 and 3 years after diagnosis BMI-SDS slightly increased, with no change during the following 3 years. Patients' BMI-SDS 6 years after diagnosis was similar to that of their parents and siblings, was not associated with age or pubertal stage at diagnosis, ethnicity or metabolic control, and was higher in females (0.53±0.74 vs 0.27±0.82, p=0.02)and in those who kept diabetes a secret. Longer duration of insulin pump therapy was the main clinical factor associated with lower BMI-SDS (R= -0.2375, p< 0.025).
Conclusions: Six years after diagnosis of T1DM in pediatric patients, BMI-SDS was in the normal range in most patients and similar to that of the parents and siblings. Longer duration of insulin pump therapy was the main clinical factor associated with lower BMI-SDS. Prospective studies including data regarding nutrition and physical activity are needed.

P2-d1-859 Glucose Metabolism 6

18F-DOPA PET and enhanced CT imaging for congenital hyperinsulinism: our experience of using oral sedation

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Background: Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycaemia in infants and children. Histologically there are two subgroups, diffuse and focal. Fluorine-18-L dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET/CT) helps to differentiate focal from diffuse CHI.
Objective and hypotheses: To evaluate the feasibility of using ^{18}F-DOPA PET/CT for the diagnosis of focal or diffuse CHI under oral sedation. To look into the protocol of performing these images.
Methods: 22 ^{18}F-DOPA PET/CT and contrast enhanced CT imaging scans were performed on 18 consecutive patients with CHI (median age 2.1 yrs). All medications including octreotide and glucagon were discontinued 48hours before the scan. Single bed position PET/CT images over the pancreas were acquired under light sedation with oral chloral hydrate (dose 50mg/kg). Four PET dynamic data scans were acquired at 20, 40, 50 and 60 min post injection for duration of 10 min each. Results were assessed by visual interpretation and quantitative measurements of SUVs (standardized uptake values) in the head, body and tail of the pancreas.
Results: Of the 18 patients, 13 showed diffuse and 5 showed focal ^{18}F-DOPA PET pancreatic uptakes. Five patients had an accumulation of ^{18}F-DOPA in the pancreas and a SUV ratio value
of > 1.5, indicating focal disease. The remaining thirteen patients had diffuse accumulation
of ^{18}F- DOPA in the pancreas (SUV ratio < 1.3). All the children tolerated oral sedation well. All patients diagnosed with focal lesions underwent surgery and were cured eventually.
Conclusions: ^{18}F-DOPA PET/CT offers excellent differentiation of focal from diffuse CHI and enhanced CT technique permits precise preoperative localisation of the lesion and anatomical land-marks. Also, excellent qualities of images were obtained after giving oral sedation (chloral hydrate) in all children without need of general anaesthesia.

P2-d2-860 Glucose Metabolism 7

Clinical and genetic characteristics of Turkish patients with congenital hyperinsulinism

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Background: Most common cause of congenital hyperinsulinism of infancy (CHI) is mutations in K_{ATP} channel.
Objective: To investigate the clinical characteristics of patients with CHI.
Methods: 21 patients (0.04-17.08 years) were included in the study. K_{ATP} channel (*ABCC8*, *KCNJ11*) and/or *HNF4A*, *HADH*, *GCK* gene sequence analysis was performed in 17 patients.
Results: Ten parents were consanguineous. Seven infants were born large for gestational age. Hypoglycemia was found in first 24 hr of life in 9 patients. During hypoglycemia [blood glucose 37.5 (15.5) mg/dL] median (IQR) serum insulin and C-peptide levels were 11.38 (13.07) µIU/mL and 2.5(3.55) ng/mL, respectively. Nine of 17 screened patients (52%) were positive for ABCC8 mutations. One patient and his parents was positive for novel HADH mutation (c.636+471G>T p). Family members were also screened in 8 families for K_{ATP} channel mutation. In one family, sister of proband was also affected; both had novel ABCC8 missense mutations (Exon 10, c.1479T>A). In another family, proband had compound heterozygous novel missense mutation in ABCC8 (maternal: Exon 37,c.4454G>A; p.Gly1485Ala; paternal: Exon 16, c.2176G>A; p.Ala726Thr). Novel missense mutation in ABCC8 (Exon 39,c.4687C>Ap.Pro1563Thr) was found in proband and his parents in a different family.Treatment with diazoxide (n:19) and/or longacting-somatostatin (n:9) had been attempted. Pancreatectomy was performed in 7 patients. Pathological examinations of pancreas revealed diffuse involvement except one patient. Five of them and their parents had mutations in ABCC8. Diabetes developed in 3 patients with ABCC8 mutations after pancreatectomy (10 yrs, 2.5 yrs and immediately after operation).
Conclusion: Since hypoglycemia has a devastating effect on central nervous system in infants, proper management of patients is important. Rapid genetic analysis for mutations in K_{ATP} channel is useful in differentiating between focal and diffuse disease in some patients.

P2-d2-861 Glucose Metabolism 7

Interdisciplinary challenges in focal congenital hyperinsulinism (CHI)

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Background: The focal form of congenital hyperinsulinism is curable by highly selective surgery. However, indispensable prerequisites are detailed informations before surgery about the genetics of patient and parents, the exact localisation of the focal lesion by ^{18}F DOPA PET/CT with its relations to the vessels in a precision down to one millimeter, and finally during surgery a scrutinizing histopathological examination of multiple tissue biopsies by frozen sections.
Methods: Between 12/2009 and 12/2012 fifteen international children aged 9,5 months (mean, range 2-35) with focal CHI have been treated by our group (Hyperinsulinism Germany International).
Results: All children showed a paternal heterozygous mutation, eleven in ABCC8 and four in KCNJ11. There were seven lesions in the pancreatic tail, three in the body and five in the head. There was no correlation of the genetic results with the localisation of the focal lesion.
Highly selective surgery under frozen section control was performed by a minimal invasive approach in seven and conventionally in eight children. In four cases a pancreatojejunostomy Roux-en-Y was carried out after a duodenum-preserving pancreatic head resection. Complications were one pulmonary embolus during surgery in a child with factor V Leiden mutation and one adhesion ileus three months after Roux-en-Y.
Highly selective surgery was curative in all children with invariably stable euglycemia thereafter. Follow-up time is 9,9 months (mean, range 2-38 months).
Conclusions: Provided that the prerequisites are fulfilled surgical therapy of focal CHI is safe and always indicated. Close interdisciplinary management is essential for a 100% cure rate.

P2-d2-862 Glucose Metabolism 7

Transient neonatal diabetes mellitus in a Turkish patient with three novel homozygous variants in the *ZFP57* gene

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Background: Neonatal diabetes mellitus is a scarce form of diabetes that is presented within the first six months of life. Nearly, 70% of these cases have loss of methylation at the differentially methylated region on chromosome 6q24.
Objective and hypotheses: In this report, we describe a Turkish male patient with neonatal diabetes mellitus caused by a loss of methylation at chromosome 6q24 and three novel homozygous mutations in the *ZFP57* gene.
Methods: Methylation-specific PCR was carried out at 6q24 and mutation analysis of ZFP57 gene was maintained by direct sequencing.
Results: Sequencing of ZFP57gene revealed the hypomethylation of chromosome 6q24 and three novel mutations(chr6:29.641.413A>T, 29.641.073 C>T and 29,640,855G>C), respectively. The latter mutation, seem to display the patients conditions because of a highly- conservative amino acid substitution in the protein. But, we are still far from identifying the effect of these variants on the function of ZFP57 and therefore its physiological effects on our patient.
Conclusions: We suggest the *ZFP57* gene as a causative factor for neonatal diabetes mellitus and should be genetically tested in the cases. Moreover, further studies including functional analysis of the detected mutations will help us to have precise information about the effect of the mutations.

P2-d2-863 Glucose Metabolism 7

Schizophrenia in adolescents and young adults with type 1 diabetes: prevalence and clinical characteristics - analysis from the prospective nationwide German and Austrian diabetes survey (DPV)

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Background: Prevalence of schizophrenia in the general population is estimated to vary between 0.5 and 1%. Antipsychotic treatment could cause side effects, which may have a negative impact on glycaemic control and metabolic risk factors in type 1 diabetes.
Objective and hypotheses: Goal was to determine the prevalence of schizophrenia in adolescents and young adults with type 1 diabetes and to explore clinical characteristics and metabolic control of patients with type 1 diabetes and schizophrenia.
Methods: Data of adolescents and young adults with type 1 diabetes up to the age of 25 years registered in the prospective, nationwide German/Austrian computer-based diabetes survey (DPV) were included in the analysis. Prevalence of schizophrenia in type 1 diabetes was calculated. HbA1c levels, BMI SDS, frequency of hypoglycaemias and diabetic complications in adolescents and young adults with diabetes and schizophrenia were compared to patients without schizophrenia.
Results: A total of 272 out of 58,399 patients with type 1 diabetes were diagnosed with schizophrenia (prevalence 0.47%). Patients with schizophrenia (63% males, 37% females) had a significantly longer diabetes duration (median 8.1 vs 5.4 years, $p< 0.01$) and a significantly higher BMI SDS (mean +0.70 vs +0.53, p=0.03). HbA1c levels were not different. Patients with type 1 diabetes and schizophrenia experienced a significantly higher number of severe hypoglycaemias ($p< 0.01$). Frequency of microalbuminuria was significantly higher in patients with schizophrenia compared to patients without schizophrenia (20% vs 12%, p=0.02). Regression analysis demonstrated that gender distribution, age, diabetes duration, BMI SDS and frequency of microalbuminuria were significantly different in patients with and without schizophrenia.
Conclusions: Adolescents and young adults with type 1 diabetes and schizophrenia had a higher BMI SDS and presented more frequently with microalbuminuria compared to patients without schizophrenia.

P2-d2-864 Glucose Metabolism 7

Serum osteoprotegerin, s-rankl and carotid intima-media thickness in the diagnosis of endothelial dysfunction in children and adolescents with type 1 diabetes mellitus

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Background: Atherosclerosis is a chronic process that begins in childhood. Diagnostic tools that identify subclinical signs of atherosclerosis include ultrasound measurement of the carotid intima media thickness (cIMT) and surrogate biomarkers. There are limited previous studies on subclinical atherosclerosis and cardiovascular risk markers in young patients with type 1 diabetes mellitus (T1DM).
Objectives: In the present study cIMT and biomarkers of the OPG/RANKL system were evaluated in association with anthropometric characteristics and other laboratory measurements in T1DM patients, in comparison to controls matched for gender, age and BMI.
Population and methods: 56 children and adolescents with T1DM were studied using anthropometric and laboratory measurements, including serum osteoprotegerin (OPG), sRANKL and cIMT and were compared with 28 healthy controls.
Results: Anthropometric, laboratory, and cIMT measurements were similar among youngsters with T1DM and matched controls. However, patients with long diabetes duration (>/7.4 years) had a trend towards higher cIMT measurements than the rest of the diabetic group
(cIMT=0.50 vs 0.45 mm, p=0.086). BMI was the only factor significantly and independently associated with cIMT (β=0.418, p=0.027 for all subjects; β=0.604, p=0.013 for diabetic patients) and with serum OPG (β=-0.335, p=0.002 for all subjects; β= -0.360, p=0.007 for diabetic patients). Serum sRANKL was not associated with any factor in the total patients group, while in those with long diabetes duration, it was significantly associated with triglyceride levels (r= 0.56, p=0.037).
Conclusions: Laboratory and sonographic findings in subjects of our study do not indicate presence of subclinical atherosclerosis in adequately controlled T1DM children and adolescents. BMI is associated with atherosclerotic burden early in life. Body weight also correlates to circulating OPG in young age, but the causes of this association remain unclear.

P2-d2-865 Glucose Metabolism 7

Ambulatory blood pressure and subclinical cardiovascular disease in children and adolescents with type 1 diabetes

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Background: Type 1 diabetes in children predicts a broad range of later health problems including an increased risk of cardiovascular morbidity and mortality.
Objective and hypotheses: The purpose of this study was to determine ambulatory blood pressure and subclinical cardiovascular disease in children and adolescents with type 1 diabetes**.**
Methods: One hundred and fifty-nine type 1 diabetic patients and 100 healthy controls were included in the study. We investigated metabolic and anthropometric parameters such as body mass index (BMI), waist circumference, fasting glucose and insulin, serum lipids, 24 h ambulatory blood pressure monitoring (ABPM), and carotis intima-media thickness (CIMT) and compared with those in control subject(CS).
Results: In children with type 1 diabetes, total cholesterol (p=0.016), and LDL-cholesterol (p=0.002) levels were higher than those of controls. In 11 % of type 1 diabetic patients, ABPM showed arterial hypertension. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) dip were 7,24±3,97% and 11,84±6,2 %, respectively, 54 study participants (33,9%) who had impaired SBP dipping and 34(21.3%) who had impaired DBP dipping. CIMT was greater in type 1 diabetic patients than CS(P 0.00). CIMT was correlated positively with Hba1c (r=0,220, p=0,037), and negatively with SBP dipping (r=-0362, p=0,020) in the combined group. In stepwise regression analysis, Hba1c and SBP dipping emerged as a significant predictor of cIMT (ß= 0,300, p=0.044, ß= 0,398 p=0,009) contributing to 15,58% of its variability.
Conclusion: These results provide additional evidence for the presence of subclinical cardiovascular disease (CVD) and its relation to hypertension in type 1 diabetic patients. They also indicate a significant relation between SBP dipping and increased arterial stiffness. Also our findings reveal significant relationships between HBA1c cardiovascular changes and underline the importance of glucose control to predict CVD.

P2-d2-866 Glucose Metabolism 7

Frequency of fetal and neonatal complications in children of diabetic mothers assisted at a tertiary University Center

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Background: Increased prevalence of gestational diabetes mellitus (GDM) as well as ocurrency of pregnancy in Type 1 (DM1) and Type 2 (DM2) diabetes mellitus make studies of these conditions relevant to reduce mother-child morbimortality.
Objective and hypotheses: Evaluate implications of DM, during pregnancy, in fetal and neonatal morbimortality, according to experience at a Tertiary Center.
Methods: 93 records of pregnant diabetics aged at least 18yrs treated between 1990 and 2009 were evaluated with prior diagnosis of DM1 (group1) or DM2 (group2), and GDM (group3). Fetal and neonatal complications were analyzed for general frequency and compared to the clinical groups using the Chi-square; p< 0.05 significant.
Results: 36.55% (n:34) had DM1, 22.58% (n:21) DM2 and 40.87% (n:38) GDM. The three groups differed in age (p< 0.001), and DM1 patients were the younger. Besides, patients in group 3 had significantly more advanced gestational age at first visit (p< 0.001) compared to the other groups. Despite different types of diabetes only birth trauma (p=0.023) was more prevalent in group 1. All other complications studied were similar in the three groups evaluated. Respiratory discomfort was generally most frequent (n:21, 22.6%), followed by prematurity (n:19, 20.43%); acute fetal distress (n:12, 12,90%); premature amniorrhexis (n:11, 11.82%); fetal macrosomia and polyhydramnios (n:8, 8.60%, for each variable); abortion, birth trauma, musculoskeletal malformation and stillbirths (n:5, 5.37%, for each variable); neonatal jaundice and congenital cardiopathy (n:4, 4.30%, for each variable); diaphragmatic hernia, duodenal atresia, omphalocele and placental insufficiency (n:1,1.07%, for each variable).
Conclusions: Fetal and neonatal complications frequently occur in diabetics during gestation, and results generally are independent of type of diabetes, indicating that other factors such as tight glycemic control and carefull follow-up should be prioritized for any pregnant diabetic.

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A case report of congenital hyperinsulinism due to a focal lesion resulting from a frameshift mutation in KCNJ11

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Introduction: The authors present a case of medically unresponsive congenital hyperinsulinism due to a focal lesion. Imaging was somewhat misleading while genetic testing confirmed diagnosis and surgery was curative.
Case study: A term male infant (birth weight 3.43 kg, 0 SD) presented with seizure and severe hypoglycemia (0.6 mmol/L) on day two of life. Hypoglycemia resolved during hospitalization and he was discharged home on routine feeding.
At 15 weeks of age (weight 7 kg, >3SD), seizures recurred after fasting. Investigations revealed hyperinsulinemic hypoglycemia (serum glucose 2.9 mmol/L, β-hydroxybutyrate 0.1 mmol/L, and serum insulin 43 pmol/L). Hypoglycemia required enteral and intravenous glucose infusion rate (GIR) of 13 mg/kg/min and was unresponsive to Diazoxide (13 mg/kg/day). Euglycemia was achieved with Octreotide (12 µg/kg) and GIR of 7 mg/kg/min.
18Fluoro dihydroxyphenylalanine positron emission tomography (18F DOPA PET) scan showed intense tracer uptake in 2 focal areas in the pancreatic head and body. Pediatric Surgery resected a solitary 2 cm lesion from the pancreatic body; pathology showed focal adenomatous hyperplasia. No other lesions were identified by examination or pathology. Postoperatively, glucose remained stable on intermittent oral feeding, without medications or dextrose. Genetic sequencing showed a heterozygous paternally-inherited frameshift mutation in the KCNJ11 gene (c.240delG) not previously reported.
Conclusions: This case highlights investigations and interventions for congenital hyperinsulinism refractory to medical management. Surgery provides definitive diagnosis but procedural planning is contingent upon focal or diffuse disease. 18F DOPA PET scan suggested the presence of a second lesion, possibly due to artifact from the large body lesion. Genetic testing and surgery were consistent with focal disease and excision of a single lesion was curative.

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Increased frequency of vitamin D deficiency/insufficiency among children and adolescents with type 1 diabetes

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Background: Increased frequency of vitamin D deficiency or insufficiency has been found in warmer countries over the last years.
Objective and hypotheses: To evaluate the presence of vitamin D deficiency or insufficiency among children and adolescents with type 1 diabetes.
Methods: Total 25OHvitamin D levels were measured in 76 consecutive chil-

dren and adolescents with type 1 diabetes [36 males, mean age (SD) 13.6 (5.09) years, median disease duration 5.38 (range 0.1 to 25.3 years)] who were attending the diabetes center. PTH, calcium, phosphorus, magnesium, alkaline phosphatase were also recorded. Body mass index (BMI), daily insulin requirements, HbA1c were evaluated.Children who were found to have vitamin D deficiency /insufficiency were treated with vitamin D with/without calcium supplement according to the dairy product consumption. Vitamin D and PTH levels were evaluated 3 months afterwards and at regular intervals thereafter till the levels returned to normal limits.
Results: Out of 76 patients only 21 (27.6 %) were found to have normal levels of vitamin D, 32 (42.1%) had vitamin D insufficiency and 23 (30.3%) deficiency. PTH levels were significantly lower in patients with normal levels of vitamin D compared to those with vitamin D deficiency/insufficiency (26.1±8.11 vs 31.9 ± 12.9 p=0.28) . There was no significant difference in alkaline phospatase, calcium, phosphorus and magnesium levels between patients with normal or abnormal vitamin D levels. No correlation was found between vitamin D levels, HbA1c, daily insulin requirements or BMI SDS, however, there were no obese children in this group of patients. Vitamin D levels increased significantly 3 months after treatment p=0.002.
Conclusions: Vitamin D deficiency/insufficiency is found in increased frequency among children and adolescents with type 1 diabetes even in warmer countries. Therefore, specialists should be aware of this possibility and have increased level of suspicion.

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Dynamics of glucose response curve during an oral glucose tolerance test and risk of type 2 diabetes in obese paediatric population

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Background: The shape of the glucose response curve at the oral glucose tolerance test (OGTT) has been recently described as a risk factor for type 2 diabetes in adults and Latino teens, respectively. However, efficacy of this novel marker has not been tested in other populations.
Objective and hypotheses: To analyze the relation between the glucose curve shape at OGTT and the risk for type 2 diabetes in obese pediatric population.
Methods: Retrospectively, the dynamics of glucose response curve at OGTT was discriminated in 551 obese children and adolescents [BMI>2SD (Hernández 2004); mean age 10.9±2.7 years] in two shapes: Monophasic (gradual rise in plasma glucose until a peak, followed by continued decrease) and Biphasic (two subsequent glycemic peaks). A set of known indicators for diabetes risk were compared between the two groups: HbA1c [HPLC Menarini™(normal value: 5.3±0.4%)], HbA1c>5.7% (pre-diabetes), glucose area under the curve (AUC)(mg*dl^{-1}*h^{-1}), insulin AUC (uU*mL^{-1}*h^{-1}), HOMA-IR, insulin sensivity (Matsuda index), insulin secretion (insulinogenic index), β cell function (disposition index) and impaired glucose metabolism (IFG: impaired fasting glucose, IGT: impaired glucose tolerance and UAG: undetermined alteration of glucose, ADA 2013). Statistical analysis: SPSS™17.0.
Results: Shown in Table 1. *p< 0.05.**p< 0.005

Patients Female/Age/ Prepuber	Total n=551 47%/10.9±2.7/50%	Monophasic n=281 48%/11.4±2.8/45%	Biphasic n=270 58%/10.9±2.8/56%*
BMI(SDS)	3.9±1.8	3.9±2.1	3.8±1.9
HbA1c/HbA1c >5.7%	5.3±0.2%/5%	5.5±0.3%/8%	5.17±0.4%/4%*
IFG/IGT/UAG	3.45%/3.3%/1.8%	3.56%/4.27%/3.2%	3.33%/2.59%/0.74%
Acanthosis/HOMA-IR	34%/2.29±2.8	32%/3.5±3.4	36%/3.1±2.1
Glucose AUC	13760±2634	14193.9±2857.4	13389.8±2213.9**
Insulin AUC	8272.3±5402.4	8937.4±5893.7	7571±4726.1**
Matsuda index	4.2±2.997	4.41±2.69	5.17±3.07
Insulinogenic index	1.89±1.3	1.63±2.20	2.01±1.43*
Disposition index	7.36±9.35	6.15±11.85	8.60±5.36**

[Table 1]

Conclusions: Monophasic glucose response curve at OGTT correlates exceptionally well with known risk factors for diabetes (glucose and insulin AUC, disposition index) in obese pediatric population.

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Prevalence of Wolfram syndrome is not necessarily so infrequent as generally expected

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Background: Wolfram first reported the combination of juvenile-onset diabetes mellitus (DM) and optic atrophy (OA) in 1938. With the discovery of two other essential components, diabetes insipidus (DI) and deafness (D), Wolfram syndrome (WS) is now also known by the acronym DIDMOAD. Prevalence has been estimated as 1:770000 in the UK (with a carrier frequency of 1 in 354). According to the most recent epidemiological study, WS prevalence in North India has been estimated as 1:805000.
Objective: Aim of the present study was to evaluate WS prevalence in a mountainous area of North-eastern Sicily, where consanguineous unions are not very unusual.
Population and methods: Our study population included 12 Caucasian WS patients from 7 couples and 5 unrelated families of North-eastern Sicily area, aged between 9 and 29 years (mean age 22.1 ± 5.6 years). Prevalence rates of WS in Messina district were calculated by taking into consideration both the total population and the populations included within the 0-30 year age range. We also estimated the relative prevalence of WS among patients with youth-onset insulin-dependent diabetes mellitus who are currently aged under 30 years (256).
Results: According to our findings, global WS prevalence in our district is 1:54478, whereas prevalence among individuals under 30 is 1:16890 and relative prevalence among patients with juvenile-onset insulin-dependent diabetes mellitus is 1:22.3. If only the five patients from non-consanguineous unions were considered for epidemiological purposes the frequency in our district would be around 1:130000 (1:40000 within the 0-30 year age range).
Conclusions:
a) The frequency of WS in the total population of a North-eastern Sicilian district might be estimated as 1 in around 55000 inhabitants, which is distinctly higher if compared with the frequencies reported in both UK and North-India,
b) WS is not necessarily so infrequent, as generally expected.

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Relationship between Gilbert syndrome and rate of nephropathy in patients with type 1 diabetes

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Background: Gilbert syndrome (GS) is an inherited disease caused by mutations in the UGT1A1 gene, which results in decreased activity of UDP-glucuronosyltransferase 1A1. Its worldwide prevalence is 3-7% and it is characterized by mild unconjugated hyperbilirubinaemia. Bilirubin, a powerful endogenous antioxidant, significantly attenuates endothelial dysfunction in preclinical experiments. In adult diabetic patients with GS, a markedly lower prevalence of diabetic nephropathy was documented, suggesting a beneficial effect of hyperbilirubinemia.
Objectives: To compare the prevalence of GS among individuals with type 1 diabetes mellitus (T1DM) to those without diabetes, and to compare the prevalence of nephropathy in individuals with both T1DM and GS to those with T1DM only.
Patients: The study group constituted 402 (204 female, 198 male) patients with T1DM, median age 21.0, (interquartile range, 15.7-27.9) with median disease duration 10.8 years. (interquartile range, 5.7-15.8). Determination of GS was based on the presence of unconjugated bilirubin ≥1.3 mg/dL. Prevalence was compared to 98 obese children (control), median age 15.8, whose liver function was studied. The prevalence of microalbuminuria was compared between patients with diabetes and GS (group 1) and patients with diabetes alone (group 2) in a ratio of 1:2 matched by sex, age, and duration of diabetes.
Results: Forty-four patients (10.9%) with T1DM had GS, 23(11.6%) males and 21 (10.3%) females. In the control group, 4 (4%) had GS, 2/49 (4.1%) females and 2/49 (4.1%) males. The rate of nephropathy was 14.3% vs. 11.4%

for patients with T1DM and GS compared to those with T1DM alone.
Conclusions: The occurrence of GS was almost 3 times higher among individuals with T1DM, and high compared to data in the literature. The rate of nephropathy was similar among individuals with T1DM and GS as to that of individuals with T1DM alone, suggesting no protective value to elevated bilirubin in patients with T1DM.

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Insulin pump treatment in neonates and infants below 1 year. Recommendations for initial choice of bolus and basal rate based on the experiences from the German working group for paediatric pump treatment

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Background: Diabetes is rare in young infants and neonates. In this age gruop continuous subcutaneous insulin infusion is most frequently used for insulin treatment. However, experience in treatment of this patients even in large centers due to the low prevalence of diabetes in this age is quite limited.
Objective: To select patients treated with CSII with an age below one year from the German DPV database and derive treatment recommendations regarding basal rate and bolus calculation.
Methods: For all patients in the age of less than 1 year basal rate and mealtime boluses were compared between infants with type 1 diabetes and infants with other types of early onset diabetes.
Results: 151 patients with CSII in the first year of live could be divided into 100 patients with type 1 diabetes and 51 neonates and infants with early diabetes development due to mainly neonatal diabetes. Type 1 patients require a total insulin amount of 0.63IE/kg bodyweight, other diabetes patients 0.49IE/kg bodyweight (p=0.02). Basal insulin requirement was different between the two groups (0.29IE/kg bodyweight in neonates vs. 0.24IE in later onset, p=0.004). The basal profile was quite similar to children in the age of 1-5 years. Prandial insulin was again significantly different (61% in infants with type 1 diabetes; 41% in neonatal diabetes, p< 0.0001). The pattern of mealtime bolus insulin was not different with a peak at lunch time for both, neonatal and later diabetes onset patients.
Conclusion: The presented data can be used as initial recommendations to start CSII treatment in neonates and infants. Basal rates can be calculated with the available sliding scale for children in the age of 1-5 years.

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Effective management of hypoglycaemia during a children's diabetes camp

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Background: We have shown in a randomized controlled trial that 0.3 g/kg of glucose (as tablets or juice) is the most effective treatment for mild to moderate hypoglycemia. Determining the effectiveness of this treatment regimen outside a clinical trial is important for clinical management.
Objective and hypotheses: We hypothesised that 0.3 g/kg glucose for treating hypoglycemia would be effective in a camp setting and that camp staff would adhere to the treatment protocol. We aimed to audit the treatment of hypoglycemia in this setting.
Methods: We audited hypoglycemia treatment during the 2013 Wellington regional children's diabetes camp. Leaders were educated in the treatment protocol prior to camp. An individual dose of 0.3 g/kg glucose was calculated for each child and recorded on their treatment sheet. Each episode of hypoglycemia (glucose < 4 mmol/L) was treated with this dose (as glucose tablets or solution), glucose re-measured at 10 minutes post treatment with a repeat dose if glucose remained < 4 mmol/L. A snack with 10-15 g complex carbohydrate was provided after resolution of hypoglycaemia. Data for each event was recorded by the leader.
Results: 29 children (15 boys) age 8-12 years, weight range 30-76 kg, with type 1 diabetes attended camp - 10 children on CSII and 19 on MDI insulin therapy. 106 episodes of mild-moderate hypoglycemia occurred in 28 children (0.95 episodes/child/day). Mean initial glucose was 3.18 mmol/L and rose to 4.99 mmol/L at 10 minutes (mean increase 1.81 mmol/L). Mean glucose at the next measurement was 8.8 mmol/L. Repeat treatment was required in 17/106 episodes (16%). These episodes had a lower initial glucose. Treatment followed the protocol in all cases.
Conclusions: 0.3 g/kg glucose provides effective treatment for hypoglycemia in a real-world setting and raises blood glucose by 1.8 mmol/L, without rebound hyperglycemia. A larger dose should be considered when blood glucose is < 3 mmol/L to reduce need for re-treatment.

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Italian translation, cultural adaptation and validation of the PedsQL™ 3.0 Diabetes Module questionnaire in children with type 1 diabetes (T1DM) and their parents

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Background: Quality of Life (QL) is an important health objective in T1DM management, being positively related to degree of metabolic control. Use of validated questionnaires is mandatory.
Objective and hypotheses: To assess the reliability and validity of the Italian version PedsQL™ 3.0 Diabetes Module, first translated in Italian according the MAPI Research Institute algorithm.
Methods: In a multicenter prospective observational study PedsQL™ 3.0 was given to 172 Italian children and adolescents with T1DM aged 5-18 years and 104 parents by trained psychologists.
Results: Data completeness was optimal. Item internal consistency was satisfied at 89% for child self-reports and 100% for parents proxy-report scales. Discriminant validity was satisfied for 71% of children and adolescents and for 82% of parents, respectively. An adequate Cronbach's α coefficient >70% was found for items of both reports, other than those for all the sub-scales in the child self-report scales (range 0.61 - 0.67). For the test-retest reliability, the Pearson correlation coefficients and ICCs ranged from 0.66% to 0.82% for all subscales of the child self-report.The Pearson correlation coefficients ranged from 37% to 99%, the ICCs ranged from 31% to 99% for the parents proxy-report. Factor analysis showed that the PedsQL™ 3.0 Diabetes Module for child self-report could be summarized into 10 components, which explain the 62% of the variance. For the parent proxy-report statistical analysis selected 9 factors which explained about 68% of variance. The external discriminating validity and responsiveness of the PedsQL™ 3.0 Diabetes Module summary measures were compared across gender, age, time since diagnosis and HbA1c mean values.
Conclusions: We confirm the reliability and validity of the Italian translation of the PedsQL™ 3.0 questionnaire. It is easy to understand and reduces cultural biases, supporting its use as an outcome measure for diabetes cross-national clinical trials and research.

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Increased incidence of type 1 diabetes mellitus during the pandemic H1N1 influenza in 2009 in eastern Santiago

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Background: Pathogenesis of type 1 Diabetes Mellitus (DM1) involves both; genetic susceptibility and environmental factors producing differences in the incidence of DM1 between age groups, gender and within areas of the same region. Pandemic (H1N1) 2009 flu also affected Chile beginning and having the highest incidence of the country in the middle-high income area of Santiago, with 68.4% of confirmed cases being at age < 18 yr (Torres et al. Clinical Infectious Diseases 2010; 50:860).These influenza A viruses (IAVs) cause systemic and non-systemic infection, which is the most common. Interestingly, Influenza A viruses are able to replicate only in the presence of trypsin like enzymes.
Objective and hypotheses: Influenza A viruses infection may trigger Beta cell destruction and increase incidence of DM1onset.
Methods: A retrospective observational study of new onset of (DM1) at the pediatric database of Clinica Las Condes from 1995 to 2012.
Results: Of a total of 58 patients, 44.8% had their onset between 2009 and 2010 (18,9 and 25.8% respectively), superimposed to the H1N1 influenza outbreak in the same district and age group. In 2011 and 2012, new cases corresponded to 12% of total per year. There was no difference in age at onset (median 9.7 vs.7.9, p ns), gender, C peptide, glycemia, HC03, pH or diabetic panel antibody (+/-) between those patients whose onset was in this period compared to the others patients.
Conclusions: Although we did not count with confirmatory data regarding H1N1 disease in new onset DM1 subjects, the increased incidence of newly onset DM1 in this period highly suggest that H1N1 is in some way involved in the pathogenesis of type 1 diabetes. Prospective studies are necessary to illustrate this hypothesis.

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Improving diabetes management in adolescents via continuous glucose monitoring technology

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Background: Studies have shown that good glycaemic control reduces morbidity and mortality. Continuous glucose monitoring (CGM) reveals fluctuations in blood glucose that often go unnoticed when standard finger stick measurements are used. Reviewing data and trend graphs from CGM can help provide insights into the underlying causes of glucose fluctuations, allowing treatment adjustments to be made to help improve patient's glycaemic control. In addition, psychological support may benefit in increased motivation promoting better health.
Aim: To assess glycaemic control of adolescents using two tools of diabetes management, CGM and psychological support.
Methods: Retrospective analysis of 28 adolescents with CGM (16 with psychological support and 12 without) at beginning and 6 months later between May 2009 - April 2012. All adolescents with Type 1 and Type 2 diabetes on insulin therapy from age 12 - 18 years old and HbA1c > 7% were included.
Results: Overall 54% of adolescents were found to have an improvement with average reduction of HbA1c 0.9% ± 0.8 after 6 months and further reduction of 1.4% ± 1.4 in 46% of adolescents after one year. 57% of adolescents who had psychological support showed slight improvement in HbA1c with average reduction of 1% ± 0.8 as compared to 43% of adolescents without psychological support (average reduction of 0.7% ± 0.4). But after one year, 50% of adolescents without psychological support sustained average reduction of HbA1c of 1.1% ± 0.5 as compared to 38% of adolescents with support (average reduction of HbA1c 1.9% ± 1.5).
Conclusions: Our findings suggest that overall CGM usage improves glycaemic control and with additional psychological support, the improvement is only short term. Therefore, we need to develop other methods of engaging adolescents to sustain longer period of improvement in glycaemic control.

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Congenital hyperinsulinism due to homozygous *ABCC8 in a* 47 XYY child

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Introduction: Congenital hyperinsulinism (CHI) is the most common cause of hypoglycemia during the newborn and infancy period.It is characterized by unregulated secretion of insulin from pancreatic beta cells in relation to the blood glucose concentration.The incidence is 1 in 50.000 births.
Objective and hypotheses: To report a male patient with sever persistent hypoglycemia hyperinsulinism.
Case study: A male infant was born at full term by Caesarean section, the second child of consanguineous parents, weighing 4 kg. The older child had died due to hypoglycemia. On the 3rd postnatal day the baby had an episode of cyanosis and desaturation and was found to have unrecordable blood glucose. Subsequently fasting insulin was 11.8 u/ml with paired glucose 21mg/dl, insulin/glucose ratio 0.56 (normal < 0.25),fasting c- peptide 1.2 ngm/ml (0.33-3.81), plasma lactate 1.3 mmol/l(0.5-2.2),serum beta OH butyrate 0 mg/dl (0-0.4),serum 60 µg/dl(6-16), ACTH 181 pg/ml(n < 56),GH 6.5 ng/ml, (up to 10), urine PH was 6 with no reducing substances. Serum free fatty acid was 0.32 nMol/L (0.1-0.6). Karyotype showed a 47,XYY pattern. Molecular genetic studies showed a homozygous *ABCC8* c.2524C>T, p.Arg842Ter (p.R842Ter) nonsense mutation, with heterozygosity in both parents. The infant was treated with Octreotide injections (5 µg/kg/6h) and now aged 3 years old has reasonable glycaemic control with glucose values >60 mg/dl but major feeding difficulties so that he is unable to take solid food.
Conclusions: Understanding the molecular mechanism of how mutation in the *ABCC8* gene cause hyperinsulinemia hypoglycemia may provide new insights into pancreatic beta- cell physiology and may help in management.

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Indeterminate glucose tolerance in youth with cystic fibrosis: transient decline in body mass index z-score

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Background: Indeterminate glucose tolerance (INDET), defined as BG ≥ 200 mg/dl at 30 or 60 minutes of an Oral Glucose Tolerance Test (OGTT) has been negatively associated with forced expiratory volume in 1 second percentile (FEV1%) when compared to subjects with normal glucose tolerance (NGT). A decline in weight preceding the diagnosis of INDET has been reported in adolescents with CF. The long term effects of INDET have not been extensively studied.
Hypothesis: We hypothesized that subjects with INDET will have a greater decline in body mass index z-score (BMIz) and FEV1% compared to NGT at 2 and 4 years from baseline.
Methods: We performed a retrospective chart review of subjects with CF between ages 6 and 18 years from January 1, 2004 to December 31, 2011 at Cincinnati Children's Hospital Medical Center (CCHMC). Subjects with other forms of glucose intolerance were excluded from the study. An analysis of covariance (ANCOVA) was used to assess the change in BMIz and FEV1%, 2 and 4 years from baseline in NGT and INDET groups.
Results: Similar to previous reports, the frequency of INDET was 22%

(38/174) and that of NGT was 56% (98/174). There was no difference in baseline characteristics including age, gender, race, CF mutation, BMIz and FEV1% between the INDET and NGT groups. There was a decline in BMIz at 2 years, but not at 4 years in subjects with INDET compared to those with NGT. Absolute FEV1% declined in INDET and NGT groups, though the difference between the two groups was not statistically significant.
Conclusions: Our results show a decline in BMIz 2 years after diagnosis of INDET in this pediatric CF population. We suspect that prompt nutritional intervention resulted in the improved nutritional status at 4 years. Further study is required to completely define the risk profile of INDET in CF.

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Genotype, phenotype and outcome of Vietnamese patients with congenital hyperinsulinism: a report of 41 cases

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Background: Hyperinsulinemic hypoglycemia (HH) is a consequence of unregulated insulin secretion by pancreatic β-cells. Congenital HH is caused by mutations in genes involved in regulation of insulin secretion (*ABCC8*, *KCNJ11*, *GLUD1*, *CGK*, *HADH*, *SLC16A1*, *HNF4A* and *UCP2*).
Objective and hypotheses: To identify mutations of *ABCC8*; *KCNJ11*, *HNF4A* and *GLUD1* in Vietnamese patients with congenital HH, to describe phenotype - genotype correlation, and to evaluate outcome.
Methods: This is a case series study including phenotype, genotype characteristics and outcome. 41 Vietnamese probands with congenital HH were analyzed for alterations in *ABCC8; KCNJ11*, *HNF4A* and *GLUD1*. All exons of these genes were amplified from genomic DNA and directly sequenced.
Results: 22/41 (54%) cases without identified mutations of *ABCC8; KCNJ11*, *HNF4A* and *GLUD1* were stable with medical treatment (diazoxide-responsive congenital HH). Sixteen probands (39%) had mutations in the *ABCC8* and no mutation in the *KCNJ11*, *HNF4A* and *GLUD1*. Their blood glucose levels were normal after nearly total pancreatectomy or resection of focal lesion by laparoscopy. Altogether, 9 different *ABCC8* mutations including three novel alterations
(p.F686I, p.I395F and p.G1379S) and six reported mutations (p.F686S, IVS27-1G>A, p.R999X, c.1467+5G>A, p.R934X and p.S1387del) were identified. One case of responsive with diazoxide had partenal inherited mutation in *KCNJ11* [c.482C>T (p.A161V)] and one case of unresponsive with diazoxide needed octreotide until 5 months of age who had homozygous mutation in *KCNJ11* [c.185delC (p.T62fs)]. One case of responsive with diazoxide had a novel mutation and maternal inheritance in *HNF4A* [c.659T>C (p.L220P)].
Conclusions: Our results extend the knowledge of the molecular genetics, phenotype and outcome behind congenital HH in Vietnam.

P2-d3-880 Glucose Metabolism 8

Low levels of plasma free fatty acids and monounsaturated fatty acids are associated with insulin resistance in obese children

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There are few and contradictory data on the association between free fatty acid (FFA) levels and insulin resistance in children. However, it is accepted that the origin of insulin resistance in obesity lies on an increased supply of FFA. The aim was to determine the association between fasting FFA levels, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and insulin resistance in obese children.
We studied 45 obese children (23 females/22 males), BMI≥p95 (NCHS) with an average age of 12.1±1.2 years. A venous blood sample was collected to measure fasting total FFA levels, SFA (myristic, palmitic and stearic acids) and MUFA (oleic and linoleic acids) by HPLC. Plasma glucose, insulin and lipids were also determined. Insulin resistance was estimated by the homeostasis model assessment (HOMA-IR).
The mean BMI was 29.8±5.7 and BMI Z-score 2.1±0.4. Fasting FFA levels were: total FFA 402.5±149.0μM, SFA 148.8±46.8μM, myristic 9.2±2.3μM, palmitic 91.4±34.3μM and stearic 48.2±15.0μM; MUFA 253.7±109.9μM, oleic 170.5±78.8μM and linoleic 83.2±33.3μM. Mean plasma levels were: glucose 94.6±10.8mg/dL, insulin 23.9±16.2mU/mL and HOMA-IR 5.7±4.2. Triglyceride concentration was 127.3±45.8mg/dL and HDL-C was 44.9±11.9mg/dL. Children were grouped by total FFA tertiles; the lowest tertile showed a MUFA/SFA ratio significantly minor (1.5±0.4, $p< 0.005$) and a significantly higher insulinemia (35.9±20.0 mU/mL, $p< 0.005$) than the highest tertile
(2.0±0.4 and 20.1±12.1mU/mL, respectively). The lowest tertile showed a total FFA level of 252.3±63.6μM, MUFA 149.2±42.8 μM and an HOMA-IR of 8.7±5.0 compared to the highest tertile with a total FFA level of 579.8±72.4μM, MUFA 385.4±63.5μM and an HOMA-IR of 5.0±3.7.
Lower total FFA and mainly MUFA were significantly associated with higher insulin levels and insulin resistance in obese children. These results agree with studies which suggest that FFA release from adipose tissue could be suppressed by elevated insulin concentrations.

P2-d3-881 Glucose Metabolism 8

Two cases of congenital central hypoventilation syndrome with a PHOX2B gene mutation complicated by hyperinsulinemic hypoglycaemia

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Background: Congenital central hypoventilation syndrome (CCHS) is a rare disorder characterized by an impaired automatic control of breathing and autonomic nervous system dysregulations. Heterozygous mutations of the PHOX2B gene are responsible for the disease. The gene is expressed in neural crest-derived cells. To our knowledge, 7 cases including ours of CCHS with heterozygous mutations of the gene have been reported to be complicated by HH.
Case report: We report 2 pediatric cases of CCHS with a heterozygous PHOX2B gene mutation complicated by Hyperinsulinemic Hypoglycemia

(HH). Both of them were diagnosed as CCHS and Hirschsprung's disease in neonatal period because of their episodes of severe apnea and results of rectal biopsy. The complication of HH was diagnosed based on their hypoglycemic episodes (blood glucose levels were 49 mg/dL and 39 mg/dL) and simultaneous high serum insulin levels (3.3 µg/mL and 19 µg/mL) in infancy. A heterozygous 27-polyalanine repeat expansion mutation in the PHOX2B gene was confirmed in both cases. PHOX2B gene products are supposed to regulate the secretion of insulin from endoderm-derived pancreatic beta cells by two mechanisms. First, this gene suppresses the function of the transcriptional factor NKX2.2, which accelerates the differentiation and proliferation of beta cells. Second, it activates dopamine beta-hydroxylase gene and accelerate the synthesis of norepinephrine in ectoderm-derived sympathetic nerve cells, thereby inhibiting insulin secretion by the pancreatic beta cells.
Conclusion: Inactivating mutations of the PHOX2B gene are supposed to result in the impairment of these two inhibitory mechanisms of insulin secretion, which leads to HH.

P2-d1-882 Glucose Metabolism 9

Effect of 2012 earthquake on glycaemic control in children and adolescents with type 1 diabetes: the experience of Modena, Italy

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Background: Coping with diabetes involves schedules and planning in daily routine. A life-threatening disaster such as earthquake may seriously affect its management.
Objective: To examine the short-term influence of Modena's earthquake occurred in May 2012 (magnitude 5.9 on the Richter's scale) on glycemic control and insulin requirement among local children and adolescents with type 1 diabetes (T1DM).
Methods: We retrospectively collected auxological, medical (dose of insulin, Ins) and biochemical data (glycosilated haemoglobin, HbA1c) from 132 children and adolescents with T1DM (12.15±4.75 yrs; duration of T1DM 67.43±48.97 months) 6 months before (PreE) and 6 months after the earthquake (PostE). Data were analysed according to residence [Epicentre (E) and surroundings area (S)].
Results: No changes in HbA1c and Ins were documented between PreE and PostE in the total population (8.29 ± 0.95 vs 8.30 ± 1.04%, p 0.90; 0.83 ± 0.25 vs 0.83 ± 0.24 UI/kg/die, p 0.35, respectively) and in E and S subgroups. Nevertheless, HbA1c increased in 16 of 37 patients living in E (44%) and in 43 of 95 of those living in S (45%). At PostE, patients on continuous subcutaneous insulin infusion (CSII) showed a lower HbA1c respect to those treated on multiple daily injections (MDI) (7.84±0.63 *vs.* 8.37±1.07, p 0.04). Multiple regression analysis, performed only in patients with an increase rate of HbA1c more than 0.5%, identified the duration of T1DM as negative predictive factor for the increase of HbA1c. The incidence of microalbuminuria increased in postE (6 *vs.* 12 cases).
Conclusions: Despite an increase of HbA1c in about half of our population, Modena's earthquake did not significantly affect the glycemic control of our patients because it did not compromise food stocks and availability of medications and equipment. Differences between CSII and MDI and the increase of microalbuminuria were hardly explainable, but the stress of dealing with the aftershock may contribute to them.

P2-d1-883 Glucose Metabolism 9

Neurocognitive and neuroimaging profile in children with hyperinsulinaemic hypoglycaemia and ketotic hypoglycaemia

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Background: Children with hyperinsulinaemic hypoglycaemia (HH) are at a high risk of brain injury, as they lack ketone bodies (KB) that are an important source of alternate fuel for the brain during hypoglycaemia. In contrast children with ketotic hypoglycaemia (KH) are believed to be neurologically protected, due to the presence of abundant ketone bodies during hypoglycaemia.
Objective and hypotheses: To investigate and compare the neurocognitive and the neuroimaging profiles of children with HH and KH (used as a control group).
Methods: The neurocognitive profile of 21 children with HH was compared to a group of 14 children with KH, using a combination of standardised tests to investigate intelligence quotient (IQ), memory, attention, academic attainment and movement. The structural integrity of the brain was evaluated using conventional magnetic resonance imaging (MRI).
Results: HH group underperformed significantly, relative to the KH group in the tests for intelligence (mean score 89.3 in HH vs. 100.5 in KH), perceptual reasoning (mean score 91.9 in HH vs 105.8 in KH), memory (mean score 93.1 in HH vs. 110 in KH), sustained attention (mean score 81.8 in HH vs. 91.7 in KH) and manual dexterity (mean score 81.1 in HH vs 95.3 in KH).
Neuroimaging revealed abnormal scans in both HH (8/21) and KH (5/14) groups. Abnormalities of the hippocampus (28.5% in HH vs 7% in KH), focal white matter (WM) lesions (14% in HH group and KH group) and diffuse WM lesions (33% in HH and 28.5% in the KH group) were reported. Mild global reduction of WM and unilateral WM reduction were seen in both groups. Moderate and severe global WM reduction was seen only in the HH group.
Conclusions: Children with hypoglycaemia are at greater risk of white matter injury. Children with HH manifest widespread cognitive deficits that may be secondary to white matter injury.

P2-d1-884 Glucose Metabolism 9

Hypoglycaemia: an unrecognised problem in cystic fibrosis (CF) patients unmasked by continuous glucose monitoring (CGM)

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Backround: Early diagnosis and treatment of CFRD (Cystic Fibrosis Related Diabetes) is important. CGM has the potential to diagnose glucose abnormalities earlier than oral glucose tolerance test (OGTT).
Objective: In this study we aimed to compare CGM vs standard OGTT in determining glucose abnormalities in CF patients.
Method: 44 CF patients(29 F) who are older than 5 years, who did not have any acute exacerbation for the last one year and no systemic steroid usage underwent OGTT followed by CGM for three days and the results were compared. The patients (pts) were classified according to OGTT and the CGM results.
Results: CGM results were grouped as hypoglycemia, hyperglycemia and both hypo and hyperglycemia.

		OGTT			CGM		
Classification of OGTT	n(%)	Mean age	Hypo-glycemia BG<60 mg/dl (n)	Mean BG (mg/dl)	Hypo-glycemia BG<60 mg/dl (n)	Hyper-glycemia BG>200 mg/dl (n)	Hypo & Hyper-glycemia (n)
Normal	26 (%59)	13	4 (%9)	108,8 ±14,1	5 (%11,3)	7 (%15,9)	5 (%11,3)
IFG	3 (%7)	13,3	1 (%2,3)	115 ±8,4	1 (%2,3)	1 (%2,3)	0
Indeterminate	5 (%11)	13,7	1 (%2,3)	127,6 ±32,4	1 (%2,3)	2 (%4,5)	1 (%2,3)
IGT	4 (%9)	15,8	0	125,7 ±6,8	0	4 (%9)	0
CFRD FH (-)	6 (%14)	14,7	0	122,6 ±19,7	1 (%2,3)	2 (%4,5)	3 (%6,8)
Total	44	13,6	6 (%13,6)	114,4 ±17,0	8 (%18,2)	16 (%36,4)	9 (%20,4)

[Indeterminate: 60.min BG≥200 mg/dl in OGTT]

Although no patient had CFRD with fasting hyperglycemia (FH+) 6 pts were diagnosed with CFRD without fasting hyperglycemia (FH-) by OGGT. In these 6 pts,CGM showed hyperglycemia in 2,hyper and hypoglycemia in 3 and hypoglycemia only in 1 pt. On the other hand,in 26 pts who had normal OGTT, CGM showed hyperglycemia in 7, both hypo-and hyperglycemia in 6, and hypoglycemia only in 1 pt. The frequency of hypoglycemia in OGTT was %13.6 and this result was compatible with other OGTT studies.However, CGM showed more frequent hypoglycemia (%38.6).

Conclusion: There are differences in detecting glucose abnormalities in CF by OGTT and CGM. CGM is a useful tool especially to determine hypoglycemia in CF patients which might be missed by OGTT. We suggest that CF patients should be evaluated by CGM especially if they are to be started /or on insulin treatment to detect and prevent hypoglycemia appropriately.

P2-d1-885 Glucose Metabolism 9

Analysis of clinical characteristics and potassium channel gene mutations in 25 cases of congenital hyperinsulinism in a Chinese population

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Background: Research on clinical features and gene mutations in CHI patients from China is rare.

Objective: Analysis of clinical characteristics and potassium channel gene mutations in patients from the Han Chinese population, and analyzed phenotype-genotype relationships.

Methods: Clinical data was collected from 25 patients and *ABBC8* and *KCNJ11* genes analysis was performed. PolyPhen-2 software was used to predict the pathogenicity of mutations. The clinical data and gene mutations were characterized.

Results: There were 16 M and 9 F, with the median age of onset being 60 days(after birth to 1year and 11 months).10 patients onset in neonatal [age: 2 days (median)], 3 of them showed the first sign as weak, lethargy. Other 22 cases were onset as seizure. The insulin level were higher in neonatal onset cases, 18.35 μIU/ml V.S 10.35 μIU/ml (Z=-2.208, p=0.027). About 60% patients had responded to dioxide based on feeding. There were no significant differences on birth weight, onset age, insulin level and with or without gene mutations between groups of respond or not to dioxide. 50% patients had brain damage when 2 years old. Mutations were identified in 9 cases (36%). 7 (78%) had mono-allelic mutations, 5 of them inherited from fathers. 2 of 9 patients were complex heterozygote of ABCC8 gene. There were 10 mutations in ***ABCC8*** and 1 mutation in ***KCNJ11***. 7 mutations (64%) of ABCC8 (Y491*, Q664*, C1000*, R 1217K, W1296*, F1392L, G1554D) were de novo The onset age of the patients with mutations was significantly younger than those without (Z=-2.584, p=0.01).

Conclusions: There was a high degree of heterogeneity and no clear genotype-phenotype correlation in Chinese CHI patients. The major mutations of Chinese CHI patients were KATP channel gene mutations, positive rate is 36% in this study.

P2-d1-886 Glucose Metabolism 9

Use of insulin pump tools and metabolic control in children and adolescents with type 1 diabetes

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Background: Bolus calculator (BC) and other insulin pump features have been developed to facilitate refined insulin treatment and diabetic control. However, few studies tested the effectiveness of such tools in pediatric patients with type 1 diabetes (T1D).

Objective and hypotheses: To asses the impact of the use of insulin pump tools on patients' metabolic control.

Methods: Last-month data downloaded from the insulin pump were analysed in a cross-sectional study including 70 patients with T1D (age 12.5±4.7 years, 51% males, 36% prepubertal) using CSII for at least 6 months (3.4±2.0 years). Data referred to number/type of boluses, use of temporal basal and pump suspension and the basal/bolus insulin percentage. We also analyzed metabolic control [HbA1c (HPLC-Menarini, nv 5.31±0.41%] including glycemic control and variability (global median glycemia±SD and hyper-hypoglycemia %)]. Statistical analysis: SPSS-program, 17.0-version, statistical significance $p < 0.05$.

Results: 91% patients use of the BC, 70% temporal basal (0.6±0.5 events/day), 30% the pump suspension (0.4±0.4 hours/day) and 20% the dual-square bolus. The basal/bolus insulin percentage was 39/61%. Mean basal rates and boluses per day were 6.5±1.7 and 6.5±1.8, respectively. BC was used to implement 84.0±21.9% of boluses (71.8±12.7% to cover meals, 67.4±14.0% to correct hyperglycemia). The patient decided overridden in 45.8±27.1% of BC. No differences were observed in HbA1c depending on the use of BC. HbA1c was inversely related with the number of boluses/day.

BC	Age (years)	Follow-up (years): T1D	Follow-up (years): CSII	HbA1c (%)	Glycaemia (mg/dl)	Glycaemia (SD)	Hyper-glycemia (%)	Hypo-glycemia (%)
NO	12.1 (3.6-17.9)	6.7 (2.6-9.8)	4.1 (2.0-6.9)	6.9 (6.3-8.2)	168.0 (129-170)	95 (74-99)	50.0 (37.0-56.0)	16.0 (14.0-26.0)
YES	13.1 (7.9-17.2)	6.8 (4.3-9.4)	3.1 (1.4-4.8)	6.6 (6.4-7.1)	150.5 (138-165)	67.5 (59-74.7)	46.5 (40.0-57.0)	7.0 (3.0-12.75)
p	ns	ns	ns	ns	ns	0.027	ns	0.013

[Table 1]

Conclusions: The use of BC and other pump tools allowed pediatric T1D patients under CSII therapy to achieve better metabolic control.

P2-d1-887 Glucose Metabolism 9

Clinical outcome and molecular defects of congenital hyperinsulinism

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Background: Congenital hyperinsulinism (CHI) is caused by diverse molecular genetic defects, showing varying degree of adenomatous hyperplasia of pancreatic β-cells.

Objective: This study was performed to characterize clinical course and molecular defects in CHI patients.

Methods: The study included 12 CHI patients diagnosed based on endocrine studies using critical samples. Direct sequencing of all coding exons and intronic flanking regions of KATP channel genes(*ABCC8, KCNJ11)* was done**.** Clinical courses, endocrine data, molecular studies and pathologic findings were reviewed retrospectively.

Results: All patients were born large for gestational age, presenting with hypoglycemia. Five patients unresponsive to medical treatment underwent near-total pancreatectomy. Histological examination revealed focal hyperplasia of

pancreatic β-cells in 2 patients, mixed lesion in one patient, and diffuse lesion in 2 patients. Five different mutations (p.V421GfsX74, p.R836X, p.L604P c.4412-2A>G, c.2041-21G>A) were identified in *ABCC8* in 4 patients and one mutation (p.E126X) in *KCNJ11* in one patient. Microsatellite analysis of 3 patients with focal lesions demonstrated paternal isodisomy for chromosome 11p15.1-5 region in tumor tissues. After near total pancreatectomy, hypoglycemia was improved in one patient. Insulin therapy was needed in 2 patients temporarily due to hyperglycemia. One patient with focal lesions received re-operation because of persistent hypoglycemia, resulting in euglycemia. A patient with diffuse CHI was compound heterozygous for *ABCC8*, requiring octreotide therapy after near total pancreatectomy due to persistent fasting hypoglycemia.
Conclusions: Hypoglycemic symptoms of patients with recessive mutations showed more severe than that of patients with the heterozygous KATP channel mutation. Long-term follow-up for large cohort of patients with CHI is needed to delineate clinical outcome after subtotal pancreatectomy and genotype-phenotype correlation.

P2-d1-888 Glucose Metabolism 9

Evaluation of anxiety and glicaemic control of teenagers with type 1 diabetes mellitus

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Background: Even though type 1 diabetes mellitus (T1DM) is a chronic disease with some serious hurdles during long term treatment and companying health problems; indeed, all attention is mostly given to physical disorders. Psychiatric status is important in both treatment managements and chronic course of the T1DM especially in younger ages.
Objective and hypotheses: We aimed to investigate the effect of anxiety level of teenagers with T1DM on glycemic control of these patients.
Methods: The study composed of 294 T1DM outpatient teenagers whose ages range from 11 to 18 years and their parents. Glycemic control parameters were determined as daily blood glucose measurement, insulin dosage per weight and hemoglobin A1c (HbA1c) levels of patients. State Trait Anxiety Inventory for Children, Children Depression Scale, Family Oriented Perceived Social Support Scale were applied for the teenagers and Beck Depression Scale, State Trait Anxiety Scale, Multidimensional Scale of Perceived Social Support applied for parents depression and anxiety level.
Results: State Trait Anxiety Inventory for Children showed a significant correlation with daily blood glucose level and HbA1c level ($p < 0,05$ and $p < 0,005$ respectively). Children Depression Scale and State Trait Anxiety Scale were related each others ($p < 0,0001$). Additionally, we found that Family Oriented Perceived Social Support Scale had a relation with HbA1c levels ($p < 0,0001$).
Conclusions: We found that increased anxiety level resulted in decreased glycemic control and more frequent blood glycose controls decreased the anxiety level in teenagers with T1DM. Additionally anxiety level related to depression and family support is important in glycemic control of the diabetic teenagers.

P2-d1-889 Glucose Metabolism 9

Residual beta-cell function and growth velocity in children with type 1 diabetes

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Background: Early studies in children with type 1 diabetes (T1D) highlighted a reduced linear growth, mainly related to poor glycemic control. It is still unclear whether abnormalities of growth still persist despite the optimization of therapy.
Objective and hypotheses: To determine the effects of modern treatment on linear growth, by prospectively evaluating height and weight changes in T1D children.
Methods: 104 children (53 females) have been followed up at 3-month intervals, since the onset of T1D. Height SDS, BMI SDS, daily insulin requirement, basal and pre-meal insulin dose, and glycated haemoglobin (HbA1c) levels were recorded. Residual beta cell mass at T1D onset was estimated by fasting C peptide levels. Height velocity and variations of height and BMI SDS during follow up were assessed. Correlations of growth velocity with glycemic control and residual beta cell mass were analysed.
Results: Follow up length was 4.7±1.2 years. Fasting C peptide at T1D onset was 0.36±0.49 ng/ml. Height velocity SDS during follow up was -0.03±2.02. Total daily insulin requirement was 0.8±0.18 U/kg/day. HbA1c was 7.75±1.02 %. A significant decrement of height SDS, associated with a significant increase of weight and BMI SDS were observed during follow up. At multiple linear regression analysis, height velocity SDS was not influenced by either HbA1c or insulin requirement, but it was directly related to C peptide levels at T1D onset [beta coefficient: 0.293 (95% CI from 0.271 to 2.04) - p=0.01-adjusted R squared: 0.153].

	T1D onset	End of follow up	p
Age (years)	5.93 ± 2.6	10.3 ± 2.4	<0.01
Height SDS	0.53 ± 1.0	0.3 ± 1.0	0.01
Weight SDS	0.52 ± 1.9	0.91 ± 1.5	0.03
BMI SDS	0.05 ± 1.4	0.32 ± 1.0	0.04

[Changes of growth parameters during follow up]

Conclusions: An impact of T1D on anthropometric parameters is still evident, not solely related to glycemic control. Residual beta cell mass may represent an independent factor influencing height velocity.

P2-d1-890 Glucose Metabolism 9

The efficacy and safety of long-acting somatostatin analog depot in young patients with persistent hyperinsulinaemic hypoglycaemia of infancy

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Background: The treatment for persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is aimed for reducing insulin secretion medically and/or surgically. Somatostatin(SS) analog is effective to maintain glucose levels for patients unresponsive to diazoxide. But, SS analog needs multiple injection or continuous subcutaneous infusion due to short half life.
Objective and hypotheses: To determine efficacy and safety of long-acting depot SS (Sandostatin LAR®; SS-LAR) in patients with PHHI.
Methods: Three male patients with PHHI were treated with SS-LAR, switched from continuous subcutaneous/intravenous SS injection after overlapping period. The dose was determined by the accumulated monthly dose of SS. SS-LAR was administered intramuscularly every 3-4 weeks. The initial dose was half of the calculated dose. The blood glucose levels, adverse effects on GI and biliary tract, liver were regularly monitored.
Results: Patient 1 and 2 were heterozygous for ABCC8 gene mutation transmitted from father. Patient 1 was switched from SS analog treatment to SS-LAR from day 39 at a dose of 40 μg/kg/day, until removal of focal lesion of pancreas at 5 months of age. Mild elevation of γ-GTP and bile stone was observed transiently, but remitted spontaneously. Patient 2 was heterozygous for sporadic ABCC8 mutation and has received subtotal pancreatectomy for his diffuse lesion. As hypoglycemia remained, he was treated with SS analog on pump and switched to SS-LAR at a dose of 72 μg/kg/day. His showed no particular adverse effect. Patient 3 was a premature baby and SS analog was started when he reached to term at 44 days after birth. At day 68, SS-LAR was started at a dose of 65 μg/kg/day. Biliary sludge was mildly formed. 18F-DOPA PET-CT is scheduled.
Conclusions: The long-acting depot SS is an easy, useful and safe tool for medical treatment of PHHI in infancy without affecting growth. Close observation is necessary to establish its long-term efficacy and safety.

P2-d1-891 Glucose Metabolism 9

The role of pump therapy in pregnant women with type 1 diabetes and its impact on development of fetopathy

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Background: The problem of type 1 diabetes and pregnancy is in priority, because of obstetric complications, perinatal morbidity, mortality.
Objective and hypotheses: To evaluate the role of insulin delivery methods to achieve glycemic control in pregnant women with diabetes mellitus type 1, and the incidence of neonatal fetopathy.
Methods: 18 pregnant women with diabetes mellitus type 1 (Group 1), aged 22,3 ± 2,1 years, treated with insulin pump therapy (pump "paradigm-722» (Medtronic, USA), the daily dose 43,9 ± 12,6 U / day. Comparison group - 22 pregnant women (group 2) treated with insulin in a basal-bolus regimen, aged 23 , 1 ± 1,8 years, insulin dose 49,9 ± 11, 4 U / day. Glycemic control using blood glycometers One Touch «Ultra» (Johnson & Johnson, USA), Acu-Chek Nano (Roche Diagnostics, USA). Monitoring using CGMS, i-Pro2 («Medtronic», USA). Quality of life (QoL) was assessed using the SF-36. Statistical data carried out by «Microsoft Excel»7, «SPSS»11.5.
Results: We found that HbA_1 at first in group 1 was HbA_1-7,93%, in the 2 - HbA_1-7,75%; in I trimester 6.1% and 7.4% respectively. Average daily blood glucose fluctuations was in 1 group 5,15 ± 2,63 mmol / l, in 2 - 8,54 ± 4,21 mmol / l, the maximum elevation of glucose to 11.6 ± 2,1 mmol / l and 15,8 ± 3,1 mmol / l, respectively. The incidence of hypoglycemia in the group 1 occurred in 3.6 times less than in the 2nd. Parameter vitality (VT) in pregnant women with diabetes type 1 are insulin pump therapy were higher than with mostly-bolus insulin therapy (p=0,064), respectively. Estimate the incidence of diabetic patients fetopathy one group is not registered, the 2nd group of 4 children with symptoms of diabetic fetopathy, ($p < 0.001$).
Conclusions: The introduction of insulin pump therapy is an effective mode of treatment for diabetes, which reduce the level of HbA_1, the incidence of hypoglycemia and diabetes fetopathy and improve the lives of pregnant women with diabetes mellitus type 1.

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Psychological characteristics of children and adolescents with type 1 diabetes mellitus

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Objectives: Chronically ill persons have an increased risk of greater psychological morbidity compared with general population. Type 1 diabetes mellitus (T1DM) is a chronic disease. Children and adolescents with T1DM are at particular risk for psychological problems which are associated with poor metabolic control and complications. The purpose of this study was to examine the presence of behavioral and emotional problems in children and adolescents with T1DM.
Methods: Subjects with T1DM age 6 to 18 years (n=37) and age-matched normal healthy controls (n=36) were evaluated using Korean Child Behavior Checklist (K-CBCL) and Children's Depression Inventory (CDI).
Results: Children and adolescents with T1DM had higher scores in CDI, compared with normal controls (13.0 ± 8.5 vs 6.3 ± 5.3). T1DM patients had more tendency to show depression, social problem, attention problem, delinquent behavior, aggressive behavior, internalizing problem, externalizing problem and total behavior problems of K-CBCL than controls. There were no significant differences in CDI and K-CBCL between well-controlled (HbA1c < 9%, n=16) and poorly controlled (HbA1c ≥ 9%, n=21) patients, and intensive (n=13) and conventional (n=24) therapy patients.
Conclusions: Children and adolescents with T1DM are prone to behavioral and emotional problems. Psychological evaluation and intervention are required in the management of T1DM during childhood and adolescence.

P2-d2-893 Glucose Metabolism 10

Molecular genetics in children with neonatal diabetes at Vietnam National Hospital of Pediatrics

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Background: Neonatal diabetes may be defined as hyperglycemia diagnosed within the first 6 months of life which is permanent neonatal diabetes or transient neonatal diabetes. The major causes of neonatal diabetic mellitus are gene mutation of KCNJ11, ABCC8, INS or abnormal of chromosom 6q24.
Objective and hypotheses: Determine gene mutations of 16 patients with neonatal diabetic mellitus treated in National Hospital of Pediatrics. Their DNA samples was analysed gene mutation of ABCC8, KCNJ11, INS and chromosome 6q24
Methods: Case series study, DNA was extracted from lymphocyte and analysed gene mutation by PCR, sequencing or methylation-specific PCR of KCNJ11, ABCC8, INS and Chromosom 6q24.
Results: 6 patients have heterozygous for a KCNJ11 missense mutation: one R201H (p.Arg201His), two R201C(p.Arg201Cys), one R50Q (p.Arg50Gln), one p.E292G (p.Glu292Gly), one p.E229K (p.Glu229Lys); 5 patients with ABCC8 mutations: one missense R1183W(p.Arg1147Trp), one nonsense E747X, one compound heterozygote for E747X and E128K, one compound heterozygote for splicing mutation (c.3403-1G>A), one novel heterozygous mutation for p.A1153G and a novel missense mutation p.E1507Q; three patients have abnormal of chromosom 6: one patient has heterozygosity for two different ZFP57 mutations (7450delT and 7812 C>T) as a result of bi-parental inheritance; two patients with INS mutation.
Conclusions: Determine gene mutaions for neonatal diabetic mellitus help to understand the pathology, diagnosis and chose a suitable therapy.

P2-d2-894 Glucose Metabolism 10

Insulin resistance in Chilean adolescents: the role of family history of type-2 diabetes

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Background: Family history of type-2 diabetes (FHDM) has been identified as a risk factor for major cardiovascular disorders related to insulin resistance and obesity (IR). In Chile, obesity rose from 22% to 32% in 1993-2001. Over the same period, T2D grew from 4% to 10%.
Objective: To study the association of FHDM with IR in a cohort of Chilean adolescents of mid-low socioeconomic level.
Design: In 543 adolescents from a longitudinal follow-up study, BMI, glucose, insulin, intake and physical activity (PA) habits were measured. HOMA-IR was calculated and values ≥3.3 according to national standards were considered insulin resistance (IR). We used bivariate and multivariate regression analysis to examine the association between IR and family history of T2D. Multiple logistic regressions assessed the relationship between FHDM (exposure) and the odds of IR, (outcome). Models were adjusted for potential confounders, including obesity (BMI z-score ≥2) at 5, 10 and 16 years. Variable selection for the logistic regression models was guided by the bivariate analyses.
Results: FHDM prevalence was 72.9%. Current obesity prevalence was 14.5%. Adolescents with FHDM showed higher though insignificant HOMA-IR compared to those without FHDM. We did not found significant differences in the prevalence of IR when comparing individuals with and without FHDM (9.0% vs.7.1%). FHDM was not associated with IR. Obesity at 5 (OR: 4.1 CI: 2.1-7.9), 10 (OR: 5.2 CI: 2.6-10.6) and 16 years (OR: 11.8 CI: 5.8-24.1) were significantly associated with IR. Current obesity was the major source of IR risk.

Conclusions: In our sample, the role of FHDM on IR risk was not significant. However, obesity seems to be stronger determinants of IR.
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P2-d2-895 Glucose Metabolism 10

Two cases of diabetic ketoacidosis in HNF1A-MODY linked to severe dehydration: is it time to change the diagnostic criteria for MODY?

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Background: HNF1A-MODY is a monogenic form of non-insulin-dependent diabetes caused by heterozygous mutations in the *HNF1A* gene. Diabetic ketoacidosis is presumably lacking in these patients because they do not have absolute insulinopenia. According to the current criteria, a history of diabetic ketoacidosis is an exclusion criterion for genetic testing for MODY.
Case report: We describe two unrelated probands aged 17 (patient 1), and 24 years (patient 2) with genetically confirmed HNF1A-MODY caused by heterozygous mutation p.Arg272His, and p.Ser142Phe, respectively. Both patients displayed positive family history of diabetes, and were negative for pancreatic autoantibodies. They developed severe diabetic ketoacidosis several years after the diagnosis of diabetes. Both patients were treated with insulin but their metabolic control was poor (HbA1c 15%, 140 mmol/mol and 13%, 119 mmol/mol, respectively) due to noncompliance and missed insulin injections. In both patients, diabetic ketoacidosis followed a course of recurrent vomiting with dehydration and pre-renal acute kidney injury. Their glycemia, blood pH and base excess at admission were 97 mmol/l [1748 mg/dl], 6.80, and -33 mmol/l (patient 1) and 34 mmol/l [613 mg/dl], 7.03, and -14 mmol/l (patient 2).
Conclusions: The two demonstrated cases of diabetic ketoacidosis in poorly controlled patients with HNF1A-MODY may have implications both for the need of adequate patient education, and for individual assessment of the indication criteria for genetic testing, as - although the molecular-genetic diagnosis of MODY diabetes has direct implications for patient treatment - most cases of MODY remain misclassified.
The study was supported by an institutional grant from the Czech Ministry of Health (grant NT 11402).

P2-d2-896 Glucose Metabolism 10

Poor evidence of enterovirus infection in newly diagnosed diabetic children in the area of Bologna, Italy

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Background: The incidence of Type 1 Diabetes (T1D) is increasing worldwide. Its rapid rise cannot be explained by genetics alone. Human Enteroviruses (HEV) are probably the most studied environmental factor in relation to T1D. Higher rates of HEV infection have been found in patients with T1D at diagnosis compared with controls.
Objective and hypotheses: Aim of this prospective study was to evaluate the incidence of HEV and other viruses infection in newly diagnosed children at the onset of T1D.
Methods: T1D patients diagnosed between April 2012 and February 2013 were tested for HEV, Adenovirus, Citomegalovirus and Epstein-Barr virus (EBV) IgG and IgM. In case of HEV IgG or IgM positive results, the Real-Time PCR was performed on blood, stool and saliva samples. RNA was extracted using the NucliSens easyMAG System (bioMerieux, Marcy l'Etoile, France) and a reverse transcription step was performed by RT-kit plus (Nanogen Advanced Diagnostics, Italy). cDNA was quantified using a Real-Time PCR assays (Enterovirus Real-Time Complete Kit, Nanogen Advanced Diagnostics, Italy).
Results: 20 consecutive newly diagnosed children with T1D (age range 1-14 yrs) were examined. 15 children (75%) were seronegative for HEV. 5 children (25%) were IgG positive and IgM negative and in these cases no HEV RNA was detected in the samples analyzed. In no cases IgM positive was found. Adenovirus IgG seroprevalence was 80%. In one 17-month old child an active EBV infection was documented by serological tests and confirmed by PCR.
Conclusions: These preliminary data suggest that in 75 % of cases a previous HEV infection can be excluded. HEV seroprevalence is 25%, however no viral RNA was detected in blood, stool and saliva samples indicating no active replication of the virus in these samples. Notably, in our case series the most common viral seropositivity was for Adenovirus.

P2-d2-897 Glucose Metabolism 10

Incidence rates of childhood type 1 diabetes mellitus (T1DM) in Liguria region, Italy, from 2006 to 2011

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Background: T1DM is a serious chronic disease in children, whose incidence is increasing worldwide. Liguria is the second Italian region with the highest incidence of T1DM, preceded only by Sardinia.
Objective and hypotheses: To evaluate T1DM incidence rate (IR) n Liguria in 2006-2011 period and the relationship between socio-demographic and clinical variables and clinical onset in children.
Methods: We considered patients diagnosed between 01/01/ 2006 and 31/12/2011 aged < 15 years. We used two sources (primary and secondary): primary source were Registers Unit of Pediatrics from the Hospitals of the 4 provinces of Liguria and secondary source was the review of data from patients enrolled in the lists of protected classes in the five Local Health Units. Incidence rates were standardized on the local population and the world's population in 2010, according to direct standardization.
Results: During 6 calendar years,192 cases of T1DM in subjects aged 0-14 years were diagnosed . The standardized rate by age and gender based on the world's population was 16.82/100,000/year, with a standardized rate for females of 14.52/100,000/years and for males of 18.97/100,000/years. The adjusted IR for completeness of ascertainment (crude IR/degree of ascertainment) was 17.04/100,000/year. Clinical onset in ketoacidosis (DKA) has been reported in 38% of cases. BMI-SDS was significantly lower in patients with DKA at onset of DM1 (P = 0.002). No significant difference was found in the seasonal onset and among classes of age at diagnosis .
Conclusions: We report an increased incidence of T1DM in Liguria, higher as compared with local previous data. We still observed a high frequency of DKA at T1DM clinical onset. The regular monitoring of new cases of T1DM is essential as part of a regional network for pediatric diabetes. Epidemiology allows the identification and the study of environmental pathogenetic factors and the development of diagnostic and therapeutic protocols.

P2-d2-898 Glucose Metabolism 10

Quality of life in a group of Chilean adolescents with type 1 diabetes mellitus

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Background: Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in children, the necessary measures for achieving good metabolic control may cause problems in patients' daily living activities and it may disrupt their quality of life (QoL).
Objective: To describe the QoL in a group of Chilean adolescents with T1DM.
Methods: 62 patients between 13-18 years old and their parents completed the Pediatric Quality of Life Inventory-Diabetes Module 3.0 (PedsQL™-DM version 3.0) during their routine nursing or endocrinologist visits. Clinical and demographic data were obtained from their medical records. Patients were classified as having either good or poor metabolic control if their glycosylated hemoglobin (HbA1c) was less or more than 7.5%.
Results: 53% of the patients were boys; the median age of diabetes diagnosis was 8.3 years. 85% of the patients had poor metabolic control (average HbA1c of 9.3%). Only 34% of the adolescents and 30% of the parents considered that they had a good QoL. In logistic regression analysis, the only significant variable to poor QoL was being female OR 4.16 (95% CI, 1.15 to 15.01). The concordance analysis between parents and adolescents showed 18.5% concordance for good QoL, 55.6% concordance for poor QoL, and the rest, 25.9% was discordant.
Conclusions: In this study 66% of the adolescents and 70% of the parents reported having a poor QoL. The only significant variable was being female, so it is essential to use tools aimed at assessing the QoL in adolescents with T1DM specially in female adolescents.

P2-d2-899 Glucose Metabolism 10

Identification of a novel WFS1 gene mutation in an Italian family with Wolfram syndrome

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Background: Wolfram Syndrome (WS) is a rare autosomal recessive disease characterized by Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness and caused by mutations of WFS1 gene. WFS1 is composed of 8 exons and encodes a protein called Wolframin. WFS1 mutations have been described mostly in exon 8, but some mutations have also been described in exons 3,4,5 and 6.
Aim: We report two familial cases of WS caused by a novel WFS1 mutation (c605A>G;pGlu202GlyHom) on exon 5.
Case description: A.T, first born female from non consanguineous parents. A.T.'s father affected by Type 2 Diabetes. A.T. manifested strabismus and ipovisus since the age of 3 years. Up to the age of 12 years she developed complete colour blindness and had diagnosis of ereditary optic sub-atrophy. At the age of 14 years, manifested polyuria and polydipsia and we made diagnosis of monogenic diabetes mellitus. We excluded diabetes insipidus. Thyroid function was normal, thyroid autoantibodies were absent.
Over follow up, A.T. showed good metabolic control and never complained about hearing impairment.
At the age of 16 years, A.T. was found to carry a novel homozygous mutation on exon 5 of WFS1 (c605A>G;pGlu202Gly), inherited from her parents, both carriers of the recessive gene (A.T.'s younger sister is not a carrier and is unaffected). A.T's grandmother (mother of A.T's mother) is affected by diabetes mellitus since the age of 21 years, bilateral optical atrophy and sensorineural deafness since the age of 31 years.
At the age of 64 years, during hospitalization for the onset of ataxia and psychiatric disorder (depression), she was found to be homozygous for the same mutation.
Conclusions: Our study increases the spectrum of WFS1 mutation with a novel variant. Such variant has never been described before in literature. From the study of clinical presentation in our two patients (A.T. and her grandmother), we can conclude that c605A>G;pGlu202Gly is a pathogenetic mutation.

P2-d2-900 Glucose Metabolism 10

iPro glucose sensor improves glycemic control in children and adolescents with type 1 diabetes

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Background: iPro is the new Enlite ™ Medtronic glucose sensor which has been recently available and continuously records blood glucose data. Its usefulness for patients with type 1 diabetes has not been evaluated in clinical practice.
Objective and hypotheses: To evaluate whether iPro use may improve glycemic control in patients with type 1 diabetes
Methods: Thirty two children, adolescents and young adults, 12 males, with mean age 14.3 ± 5.9 years and median disease duration 4.9 years (range 1.13-21.4 years) wore the iPro sensor for 7 days. The patients kept a detailed diary of food consumed, exercise, insulin dosing and capillary blood glucose measurements during the whole period. Data were loaded on a PC and discussed with patients or their parents after the end of this period. HbA1c before and the mean HbA1c over the last year (4 values) were compared to HbA1c 3 months after the iPro use. Furthermore, daily insulin requirements and hypoglycemic episodes were recorded before and after the iPro.
Results: HbA1c levels after the iPro use were significantly lower compared with the levels before or the average HbA1c over the last year ((7.6 ±0.76 vs 8.01±0.86, p=0.001 vs) 7.98±0.87 p=0.007 respectively). HbA1c before was not different compared to the measurements -3, -6, -9 months before the iPro use. Total or bolus daily insulin requirements were greater after the iPro use; however, the difference was not significant. (p=0.059 and p=0.079 respectively). The number of hypoglycaemic episodes was not significantly reduced.
Conclusions: The use of iPro significantly improved glycemic control in patients with type 1 diabetes and therefore is a useful educational tool**.**

P2-d2-901 Glucose Metabolism 10

Endothelial dependent vasodilatation across glucose tolerance categories in obese adolescents

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Background: Obese adolescent with T2DM and /or pre diabetes demonstrate endothelial dysfunction (ED), a key early event in atherogenesis. Flow mediated dilatation (FMD) of the brachial artery is a well validated surrogate for ED. Traditional cardiovascular risk factors (BMI, LDL-cholesterol, systolic blood pressure and smoking) have a deleterious effect on the vasculature in adolescents.
Objective and hypotheses: We proposed to delineate the relationship between glucose tolerance categories and ED in obese adolescents.
Methods: 25 adolescents with a mean age of 15.7 ± 1.5 years, BMI 35± 6 (60% female and Hispanic) underwent a 75 gram oral glucose tolerance test (OGTT). Duplex ultrasound (11MHz transducer) measured endothelium dependent vasodilatation. Reference range in our vascular lab for FMD is 5.89± 2.88% (95% CI: 4.53- 7.23).
Results: Based on OGTT results: 16 subjects had normal glucose tolerance (NGT: fasting glucose ≤ 99 mg/dl and/ or 2 hour post challenge glucose ≤ 139 mg/dl) and 6 subjects were diagnosed with pre diabetes(fasting glucose≥ 100 and/ or 2 hour post challenge glucose ≥ 140 mg/dl). Adolescents with T2DM (n= 3) had lower FMD (3.2± 2.8%) compared to adolescents with NGT (6.5± 5.08%) and of those with NGT; five had an impaired FMD (≤ 5.8%). Adolescents with pre diabetes had FMD values (9.8± 3.08%) higher

than NGT group, though differences between the glucose tolerance categories did not reach statistical significance (NGT vs. pre diabetes vs. T2DM, p= 0.26). FMD did not correlate with CVS risk factors in these adolescents. In adolescents with NGT, FMD was negatively correlated with 2 hour glucose (r= -0.6, p= 0.03).
Conclusions: Adolescents with prediabetes compared to those with T2DM appear to have preserved endothelium dependent vasodilatation. In adolescents with NGT, lower FMD predicts impaired glucose tolerance and accelerated vascular dysfunction. CVS risk factors did not appear to affect FMD in these obese adolescents.

P2-d2-902 Glucose Metabolism 10

Renal function in children and adolescents with type 1 diabetes mellitus (T1DM)

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Introduction: Diabetic nephropathy is the main cause of end stage renal disease, early detection is crucial to prevent its progression
Objective: To evaluate renal function parameters in T1DM children and adolecents and to compare with age, gender, metabolic control and diabetes duration.
Methods: A retrospective analysis of 144 T1DM < 20 years was done. Data collected: age, gender, time of diabetes onset, mean HbA1c in the last year, plasmatic creatinine, creatinine clearance (CrCl) (by Schwartz formula), and albuminuria/creatininuria rate(ACR).
Results: 144 patients were studied, 74 males, average age 13,1±3,2 (2,3-19,1 years), with a follow-up since DM diagnosis of 4,7 ± 3,6 years. Last year average HbA1c was 8,8±1,9% and 22,9% had good metabolic control based in recommended level of HbA1c < 7,5%. Mean CrCl was 160,7±39,5 ml/min males vs 139,3±36,2 in females (p=0,0003). Hyperfiltration was observed in 63,2% patients, 5,5% had microalbuminuria and 2% macroalbuminuria. There was positive correlation between HbA1c and age (r=0.2 , p=0,0051) between HbA1c and diabetes duration (r=0,16, p=0,002) and between CrCl and age(r=0,19, p =0,01) There was no correlation with CrCl neither ACR. There was no correlation between CrCl and ACR.
Conclusions: High percent of our diabetic patients had hyperfiltration, with male predominance and older age. This could be the first sign of renal involvement
preceding the appearance of microalbuminuria. monitoring is critical to preventing deterioration of renal function.

	< 5 years	5-10 years	>10 years
N	2	22	120
Gender M/F	1/1	9/11	64/56
HbA1c (%)	7,3±0,1	7,9±1,5	9,1±2
Crea Cl (ml/min)	95±16,9	152,4±37,8	167,3±33,6
Hyperfiltration (> 140ml/min)	0%	45,4%	67,5%
ACR > 30 mg/g	0%	4,5%	9,2%
ACR > 300mg/g	0%	0%	2,5%

[Laboratory parameters by age group]

P2-d2-903 Glucose Metabolism 10

The effect of sulfonylurea therapy in neonatal diabetes mellitus patients with highly heterogeneous genetic background

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Background: Neonatal Diabetes Mellitus (NDM) is a rare special type diabetes mellitus. Many genes participate in its pathogenesis. Although there are occasional case reports, no genetic clues and clinical follow-ups has been disclosed about NDM in Chinese population.
Objective and hypotheses: Our aim was to delineate clinical sulfonylurea treatment with heterogeneous genetic background.
Methods: KCNJ11, ABCC8, INS gene mutation and 6q24 methylation analysis were performed in thirteen patients. Sulfonylurea therapy was applied and the glycemic status was evaluated during the 5 years' follow up.
Results: Diabetes was diagnosed at a mean age of 64.77 ± 50.56 days (range, 1 to 178 days). At diagnosis, all the patients had hyperglycemia (glucose concentration, 7.7 to 66.7 mmol/L. The median of HbA1c was 14.84±11.06% (range, 6.1% to 52.8%) and the mean of birth weight was 2451.72±660.13g (range, 1420 to 3593g).
Two patients were found with ABCC8 gene mutation, four with KCNJ11 gene mutation, one with INS gene muation, one with GLUT2 mutation, one with 6q24 methylation defects, four without detected genes mutation. 92.31% (12/13) patients reached euglycemia with sulfonylurea except one patients with INS mutation.
Conclusions: Although the mutation spectrum is diverse, high frequency of KCNJ11, ABCC8 were found in the subjects, sulfonylurea therapy were well tolerant without evident side-effects and euglycemia were reached in most of the patients.
Acknowledgements: The genetic test was performed with the aid of Professor Sian Ellard from Royal Devon & Exeter NHS Hospital.

P2-d3-904 Glucose Metabolism 11

Transient neonatal diabetes in Spanish patients: natural evolution during the two first decades of life

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Background: Monogenic neonatal diabetes occur approximately 1 out of every 100.000 live births. There are two main clinical subtypes: the persistent permanent neonatal diabetes and the remitting one, called transient neonatal diabetes (TND). TND is due to chromosomal abnormalities of *6q24*, as well as to *KCNJ11, ABCC8 or INS* mutations. In some of these patients, diabetes may relapse throughout life but little is known respect to its long-term course.
Aim: To study carbohydrate metabolism in person which were born in Spain after 1990 and had a TND.
Patients and methodology: We have studied 15 people. Genetic analyses had been performed in Cruces Hospital. In 2012 the patients were visited by a paediatric endocrinology in 12 hospitals of Spain. A completed physical examination was performed and a blood sample was collected to analyze Hba1c and basal glucose levels; in older than 8 years, an oral glucose tolerance test was done.
Results: Mean current age of patients was 9.3±7.3; height and weight were normal (weight-SDS:-0.2±0.9 and height-SDS:-0.4±1.1). TND aetiology was: abnormalities of *6q24* in 9 person, *KCNJ11 or ABCC* mutation in 5 and *INS* compound heterozygous mutation in 1. TND data: mean insulin treatment duration was 110±84 days and 73% of patients did not presented ketoacidosis at diagnosis. Patients with *6q24* abnormalities had a lower neonatal weight-SDS (-2.8±0.2 vs. -0.6±0.5; p=0.000) and an earlier diabetes onset (10.1±5.9 vs. 55.3±11.4 days; p = 0.003).
CM results: Mean Hba1c was 5.7±0.6% (range: 4.8-6.7). Diabetes was diagnosed in 3 patients (age: 5.5, 5 and 11.5) and glucose intolerance in 4. The patients with any kind of CM alteration received insulin treatment at neonatal age during more time than the rest (145±94 vs. 62±30 days; p=0.048).

Conclusions: Carbohydrate metabolism pathology appears soon throughout life in patients affected by TND; half of them present any alteration during the first two decades.

P2-d3-905 Glucose Metabolism 11

Vitamin D level as a predictive factor of certain parameters in patients with type 1 diabetes

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Background: Several studies show there may be a relationship between vitamin D (VD) status and glucose metabolism and/or diabetic control.
Objective: The purpose of this study was to determine if there is a significant correlation between VD levels and several variables in pediatric patients with insulin-dependent diabetes. The variables investigated in this study were: hemoglobin A1c, ethnicity, BMI, insulin requirement, and presence of metformin as part of the treatment.
Methods: A retrospective chart review was done for a total of 40 pediatric diabetic patients.
Inclusion criteria were a diagnosis of insulin-dependent diabetes, age 21 years or less and having a hemoglobin A1c with a concomitant measured 25-hydroxy VD level done during the same visit.
Results: Statistics were done by regression analysis and two-sample t test analysis with equal variances depending on the parameter being studied.
Lower levels of VD correlated significantly to higher hemoglobin A1c in patients with insulin-dependent diabetes. ($p = 0.013$) Figure 1.
When VD level was compared with insulin requirement calculated as total daily insulin dose in units of insulin per day, the regression analysis resulted in a significant p value of 0.017.
When calculating insulin requirement in units per kilogram per day, compared to VD level, regression analysis showed a significant p value of 0.036.
The patients that needed the addition of metformin to their diabetic treatment had lower levels of VD ($p = 0.004$).
In our study the relation of VD levels to BMI and ethnicity was non-significant.
Conclusions: Patients with lower levels of VD were using higher doses of insulin and had higher values for hemoglobin A1c. Patients that benefited from metformin also had lower levels of VD. These findings may suggest that lower levels of VD may contribute to the need for higher insulin doses, that may be related to insulin resistance, and suboptimal glucose control in pediatric patients with insulin-dependent diabetes.

P2-d3-906 Glucose Metabolism 11

Case report: use of long-acting octreotide in a child with congenital hyperinsulinism on diazoxide

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Background: Congenital hyperinsulinism (CHI) is a common cause of hypoglycemia in infancy. The medical treatment includes use of Diazoxide, and of somatostatin analogue in Diazoxide unresponsive patient.
Objective and hypotheses: We report a first case of 14 year old girl, diazoxide responsive, who has been switched over to 4 weekly long-acting somatostatin analog lanreotide acetate (Somatuline Autogel) due to the side effects of diazoxide.
Methods: A 14 year old girl with congenital hyperinsulinism had responded well to diazoxide at the time of diagnosis. However, she continued to have hypoglycaemic episodes on reducing the dose of Diazoxide. She was on 6.5mg/kg/day of Diazoxide but had excessive hair growth all over the body and as a result had issues with the compliance. She was started on lanreotide to be given by deep subcutaneous route every 4 weeks and gradually reduced the dose of Diazoxide. She had continuous blood glucose monitoring for 1 week pre and post Lanreotide.
Results: After receiving the first dose of lanreotide 30 mg (22mcg/kg/day), her dose of Diazoxide was gradually reduced. She continued to be on small dose of Diazoxide (2mg/kg/day) until the 3rd dose of Lanreotide and was then stopped. The pain score and quality of life questionnaire were recorded at the time of first injection. Lanreotide injection was administered under local anaesthetic cream cover and pain score was 1/10. Her baseline liver function, thyroid function and IGF1 and IGFBP3 were normal. She also had normal ultrasound gall bladder (pre lanreotide). Treatment is well-tolerated, and no side effects were reported.
Conclusions: This is the first case of Congenital Hyperinsulinism who has been transferred from diazoxide to long acting Octreotide injection reported. Lanreotide acetate may be a safe and effective alternative to Diazoxide therapy in patients with CHI, offering an improved quality of life. Longer follow-up of a larger patient group is needed.

P2-d3-907 Glucose Metabolism 11

KCNJ-11 gene mutation analysis in 27 patients with infancy and early childhood diabetes mellitus

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Background: The ATP-sensitive K^+ channel (K_{ATP}) controls insulin secretion from the islet. Mutations in *KCNJ11* can cause permanent and transient neonatal diabetes. To date, more than 30 KCNJ11 mutations have been revealed to be related to the onset of NDM, most of which are responsive to glibenclamide treatment. Recent searches also revealed that some monogenetic mutations including KCNJ11 gene also account for the pathogenesis of infantile and early childhood type 1 diabetes. In the present study, we sequenced the KCNJ11 gene in 10 patients with PNDM and 17 patients with infantile and early childhood type 1 diabetes.
Objective: To do gene mutation analysis on KCNJ11 gene in 27 patients with diabetes mellitus under 3 years old so as to study the genetic onset mechanism of infancy and early childhood diabetes mellitus.
Methods: 27 patients diagnosed with infancy and early childhood diabetes mellitus and there parents were chosen as research subjects. TIANamp Blood DNA kit method technique were used to extract genomic DNA from peripheral white blood cells, PCR techniques were used to amplify the KCNJ11 gene, after which DNA direct assay techniques were used to analyze gene mutation on KCNJ11.
Results: A in-frame 15-bp KCNJ11 deletion was identified in a patient diagnosed with neonatal diabetes mellitus (c.82-96del), which result in 5 amine acids deletions (A28-R32), while no KCNJ11 deletions were found in her parents. The patient was responsive to the treatment of glibenclamide. A heterozygous c.1096G>T (G366W) mutation was identified in a patient diagnosed with diabetes at 1 year and 7 months old, and the patient's father carried the same mutation. No KCNJ11 mutations were found in other paitents.
Conclusions: The rare c.82-96del mutation on KCNJ11 can lead to neonatal diabetes mellitus in Chinese children. Also the mutation on KCNJ11 can lead to infancy and early childhood diabetes mellitus, while the onset mechanism of which were not clear.

P2-d3-908 Glucose Metabolism 11

Glycaemic profile during remission in a patient with 6q24 transient neonatal diabetes

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Introduction: Transient neonatal diabetes (TND) is a rare condition, of which 6q24 abnormalities accounts for two third of the cases. Diabetes recurs in more than half of the patients with 6q24 TND around puberty. Mechanisms causing transient diabetes in neonates with later recurrence are not yet understood, however, overexpression of the candidate genes in mice showed

reduced insulin secreting structure, suggesting reduced insulin secretion in patients with 6q24 TND as a basic defect.
Case study: A male patient aged 26 years. Neonatal diabetes was recognized at day 3, and treatment with insulin was continued until age 6 months. Diabetes recurred at 11 years old and oral hypoglycemic agents have been used for his glycemic control. HbA1c has elevated gradually and is around 8% lately. Recent genetic studies revealed 6q24 paternal duplication in this patient. He was followed by annual oral glucose tolerance test until diabetes recurrence, and indices of insulin secretion and insulin resistance were calculated. Insulinogenic index was low and HOMA-beta declined gradually during the remission period. These are indicated as markers for insulin secretion. On the other hand, HOMA-R and QUCKI, which are indices of insulin resistance, remained within the normal range.
Conclusion: Indices for insulin secretion were low, while those for insulin resistance were normal during remission in a patient with 6q24 TND, supporting the proposed hypothesis from animal studies, where reduced insulin secretion is likely to be a basic defect of this disorder.

P2-d3-909 Glucose Metabolism 11

Characterisation of cases of congenital hyperinsulinism in a tertiary paediatric endocrinology clinic: high yield from genetic testing and prevalence of dominantly inherited ABCC8 mutations

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Background: Congenital Hyperinsulinism (CHI) is a rare genetic disorder of inappropriate insulin secretion and recurrent hypoglycaemia. Ireland has a higher incidence (1:27,000) than worldwide reports. Causative mutations in at least seven genes have been found, most commonly mutations in the ABCC8 gene (40% of cases). Determining an underlying genetic mutation has implications for diagnosis and treatment.
Objective and hypotheses: To examine prevalence, genetics and phenotype of all patients with CHI attending a regional paediatric endocrinology clinic serving a population of 664,534.
Methods: Eight patients had been diagnosed with CHI, including 5 members of one extended family, 2 sets of siblings who are first cousins. Genetic testing was undertaken over a six month period in patients not already tested (n=4).
Results: A genetic mutation was identified in the 7 patients who had permanent CHI. 6 had a heterozygous ABCC8 mutation: a missense mutation (G1479R) in 5 members of the same extended family all of whom were diazoxide responsive, and a nonsense mutation (p.W998X) in a boy who had a subtotal pancreatectomy in 1997 due to diazoxide unresponsiveness. Three unaffected parents (1 mother, 2 fathers) had the same mutation as their affected offspring. One patient, who was responsive to diazoxide was heterozygous for a novel HNF4A missense mutation. Genetic testing was negative in one patient who was subsequently weaned off diazoxide by age ten years.
Conclusions: The high prevalence of patients with CHI in our clinic is largely due to one extended family with multiple affected members. The dominant inheritance and incomplete penetrance shown by lack of expression in the carrier parents in both families with ABCC8 mutations is noteworthy. Availability of genetic testing for the diazoxide unresponsive patient may have suggested a focal cause and avoided pancreatectomy. This study highlights the importance and utility of molecular genetics in clinical Paediatric Endocrinology.

P2-d3-910 Glucose Metabolism 11

Hyperinsulinaemic hypoglycaemia and brain injury in term babies with no risk factors: how long is too long?

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Background: Hyperinsulinaemic Hypoglycaemia (HH) is characterised by the unregulated secretion of insulin from pancreatic β-cells, leading to hypoketotic hypoglycaemia. Neurological damage is a major risk associated with HH. However it is not known what duration of HH leads to brain damage especially in term babies with no risk factors for HH. .
Objective and hypotheses: To describe the clinical course and neurological outcome of 3 term neonates with severe hypoglycaemic brain injury who have had no risk factors for developing HH.
Methods: 3 patients who presented in the neonatal period with biochemically confirmed HH and referred to a tertiary endocrine hospital were recruited. Detailed clinical information was collected including MRI brain reports.
Results: All three term neonates, born by normal vaginal delivery with no risk factors for HH, were discharged home after 24-36 hours of birth. Birth weight range was 2.73kg-3.46kg. All infants presented to A & E on day 3 of life with non-specific symptoms like poor feeding and lethargy. However all of them were noted to have jerky and seizure like movements. Biochemically, all had blood glucose levels less than 0.6mmols/L with raised insulin and suppressed NEFA and KB. They all successfully responded to small doses of Diazoxide. Each neonate had a MRI scan of the brain due to clinical neurological concerns that showed significant evidence of hypoglycaemic brain injury (eg. gross white matter changes with parieto occipital infarcts).
Conclusions: Term babies with no risk factors for HH are at an increased risk of brain damage. These infants with no risk factors are often difficult to identify due to non-specific symptoms. Even after three days of HH all three infants developed brain injury. These observations suggest that in some patients with HH, hypoglycaemic brain injury can occur even after short periods. Further studies are required to understand the mechanism/s leading to brain injury in these patients.

P2-d3-911 Glucose Metabolism 11

Variations in cumulative incidence of the association between coeliac disease and type 1 diabetes in Northern Italy

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Background: The association between Type 1 Diabetes Mellitus (T1DM) and Celiac Disease (CD) has been known for more than 40 years. In 2008 the group from Bologna (Salardi et al, JPGN) reported data about CD prevalence in T1DM patients of 10.6% after 1994, significantly higher than previously reported in our centre (p=0.015).
Objective and hypotheses: Aim of this study was to evaluate an up-to-dated cumulative incidence rate of the association between T1DM and CD in Northern Italy.
Methods: All newly diagnosed T1DM patients from January 2005 to December 2012 were annually screened for CD-related antibodies in 4 Italian centres in Northern Italy. If consistent positive autoantibodies patients underwent to a duodenal biopsy to confirm the diagnosis (according to Marsh classification).
Results: 1114 newly diagnosed T1DM were screened for CD autoantibodies and 89 patients were diagnosed for CD (7.9%). The centre of Bologna showed the highest cumulative incidence rate, comparable to what previously published in 2008. The whole prevalence of the association between T1DM-CD among all the patients followed by the 4 centres is of 178 patients out of 1727 (10.3%). In 2% of patients CD was diagnosed before T1DM, in 61% first CD

autoantibody positivity was found at T1DM onset. In the other cases CD was diagnosed within the first 5 years from T1DM onset.

	New T1DM cases	New CD cases	T1DM+CD cumulative incidence
Bologna	146	18	12.3%
Turin	378	23	6.1%
Trento	132	13	9.8%
Florence	458	35	7.6%

[Local centre T1DM-CD incidence]

Conclusions: The whole cumulative incidence and prevalence of the association between T1DM and CD in Northern Italy did not differ from what reported in literature, although in the upper range. We found local differences between the centres, probably due to the involvement of environmental factors. The majority of CD cases were diagnosed at the onset of T1DM.

P2-d3-912 Glucose Metabolism 11

The incidence trend of type 1 diabetes mellitus in children in Beijing based on hospitalization data during 1995-2010

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Background: The incidence of type 1 diabetes in children younger than 15 years is increasing.
Objective and hypotheses: Our aim was to assess the incidence trend of T1DM since 1995 in Beijing children and to predict the number of T1DM in the future.
Methods: We collected the newly diagnosed T1DM children younger than 15 years in Beijing Children's Hospital in 1995-2010 and calculated the incidence of Beijing children with T1DM. We defined it as the estimated incidence rate.
Results: The standard average estimated incidence was 1.3/100 000 during 1995-2010, increasing from 0.57/100 000 to 2.25/100 000. The estimated incidence increased in all age groups compared between 1995-2002 and 2003-2010: from 0.24/100 000 to 0.57/100 000 in 0-4 yrs, from 1.31/100 000 to 2.12/100 000 in 5-9 yrs, from 1.25/100 000 to 1.86/100 000 in 10-14 yrs. The predicted number of new T1DM cases will increase 1.1 times and the percentage distribution of new cases will be 34.89% (< 5 yrs), 37.08% (5-9 yrs) and 28.03% (10-14 yrs) in 2020.
Conclusions: The T1DM incidence of Beijing children definitely increased. The greatest increased age group of estimated incidence was the younger than 5 yrs. The predicted new T1DM cases will be more even distribution across whole age-groups.

P2-d3-913 Glucose Metabolism 11

New technologies for promoting hypoglycaemia self-management in type 1 diabetic children

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Background: A correct understanding of insulin metabolism by diabetic children is essential for guaranteeing a good quality of life and a constant adherence to an appropriate therapy, in order to prevent future complications. Therefore it is important to adopt new strategies for motivating and making the learning process the most useful as possible, above all for teenagers.
Aim: To describe how an informatic game can be used for educating young diabetic patients, helping them to self-manage their clinical conditions, to prevent serious hypoglycaemic events and above all to reduce psychological burdens.
Methods: In the last years, the team of Diabetes Division of Department of Metabolic Diseases and Medical Genetics of "Giovanni XXIII" Hospital (Bari) worked together with a team of researchers from the Department of Informatics (University of Bari) designing and implementing an innovative informatic game in order to make therapy learning process easier, more intuitive and stimulating.The goal of our game ("Treasure Hunter") was to allow the acquisition of self-management skills in children aged between 8 and 12 years. This game was very useful for training young diabetics, teaching them how to self-manage their clinical condition. Nevertheless, "Treasure Hunter" was a useful tool also for their unaffected friends, making them aware of the proper lifestyle for diabetic children. In order to measure the learning efficacy and the utility of our game, we performed a pilot study which included 11 patients followed by Diabetes Division of the Department of Metabolic Diseases and Medical Genetics at the "Giovanni XXIII" Hospital (Bari).
Conclusions: Our pilot study confirmed the literature evidences about the learning efficacy: using the game dimension and the interactive approach, our young patients learned how to prevent hypoglycaemic events and to handle their therapy with more enthusiasm.

P2-d3-914 Glucose Metabolism 11

Focal congenital hyperinsulinism due to a novel mutation of ABCC8 gene

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Introduction: Congenital hyperinsulinism (CH) is a group of metabolic disorders commonly associated with inactivating mutations of the ABCC8 and KCNJ11 genes encoding the β-cell ATP-sensitive K+ channel. Histologically, diffuse and focal forms are distinguished. Diazoxide-unresponsive diffuse forms can be caused either by two compound heterozygous recessive mutations or by a single dominant mutation of ABCC8 or KCNJ11. Diazoxide-unresponsive focal forms result from one paternally inherited ABCC8 or KCNJ11 mutation and loss of the maternally inherited 11p15 region.
Case study: We report on 1.3 years old patient with a focal form of CH carrying a novel missense p.Val17Ala mutation of the ABCC8 gene.
The patient is the first child of healthy nonconsanguinuous parents. Her clinical appearance and development were normal until the age of 5 months when she presented with somnolence and irritability in severe hypoglycemia. The results of laboratory evaluation during hypoglycemia resembled CH (blood glucose 1.9 and 1.5 mmol/l, insulin 6.1 and 12.3 mU/l, C-peptide 0.58 and 1.02 nmol/l, no ketone bodies, normal lactate). Continuous glucose infusion (2-6 mg/kg/min) was required to maintain normoglycaemia. She was diazoxide unresponsive. Subcutaneous octreotide injections allowed discontinuation of glucose infusion. Sequence analysis identified the novel missense p.Val17Ala mutation of ABCC8 gene in the patient, inherited from her clinically unaffected father. ^{18}F-DOPA PET scanning confirmed focal lesion in the pancreatic tail and she underwent resection of the lesion resulting in complete recovery. At the age of 1.3 years she is free of hypoglycemia and medications and her development is normal.
Conclusions: We report on a patient with a focal form of CH carrying the novel p.Val17Ala mutation in the ABCC8 gene, inherited from her clinically unaffected father. Our case emphasizes the need of prompt molecular analysis which facilitates further diagnostic and therapeutic decisions.

P2-d1-915 Glucose Metabolism 12

Screening results for microvascular complications according to recent consensus in adolescents with type 1 diabetes

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Objective: Screening of long-term micro and macrovascular complications is one of the most important part in diabetes care. Our aim was to investigate diabetic complications and related risk factors in adolescents with type 1 diabetes mellitus (T1DM) after 11 years of age or after 2-year's diabetes duration according to current global consensus of International Society for Pediatric and Adolescent Diabetes (ISPAD) and International Diabetes Foundation (IDF).
Methods: The study included 155 adolescents with T1DM (67 male, 88 female), mean aged 14.4±2.1 years and with mean diabetes duration of 6.3±2.9 years. A cross sectional study was done among type 1 diabetics after 11 years of age or after second years of diabetes. Patients were screened for diabetic nephropathy, retinopathy and peripheral neuropathy.
Results: Mean HbA1c level was found 8.4%. The prevalence of microalbuminuria and peripheral neuropathy were 16.1% and 0.6%, respectively. None of the patients had diabetic retinopathy. Dyslipidemia and hypertension rates were 30.3% and 12.3%, respectively. Risk factors associated with microalbuminuria were hypertension, higher HbA1c levels, longer diabetes duration and dyslipidemia.
Conclusion: Annual complication screening for diabetic nephropathy should be done 2 years after diabetes duration in patients with T1DM. However, retinopathy and neuropathy screenings may be postponed after 5 years of diabetes, for in cases with good metabolic control and without hypertension or dyslipidemia. Special attention is needed for early diagnosis and treatment of hypertension and dyslipidemia as well as achieving a better metabolic control.

P2-d1-916 Glucose Metabolism 12

The effect of education on glycaemic parameters in children with type 1 diabetes mellitus

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Background: Education of patients with diabetes and their parents is essential in every programme, because it has important role in making the patient an active participant in achieveing key therapeutic goals of the treatment of type 1 diabetes. Therapeutic education programme need to be structured taking into account therapeutic scheme and need to be adapted to patients needs and at the same time showing its effectiveness.
Objective and hypotheses: This study was designed to evaluate the effect on glycated hemoglobin (A1C) of a structured intervention in type 1 diabetes patients. We prospectively conducted interactive 5-day education programme based on Düsseldorf model of functional insulin therapy for type 1 diabetic patients on Department for child diseases of Cantonal hospital.
Methods: We analized 67 type 1 diabetes patients, mean 11±0.68 years of age, 43 female and 24 male patients. The programme was lead by trained team of Diabetes Specialist and Nourse. All subjects complited knoweldge test about diabetes at beginning and at the end of education (30 questionare). Subjects were evaluated for total daily insulin, and HbA1c at baseline, and 3, 6, 9 and 12 months after the education programme.
Results: Results of knowledge test after education have showen higher knowledge at baseline. At the end of education programme average total daily insulin dose was significantly lower. There was a 1,6 % reduction in HbA 1c over 6 month, and 1,2% over 12 months in comparison to baseline values.
Conclusions: Structured education programme of functional insulin therapy is associated with improved glycaemic control in type 1 diabetes patients and their parents. It motivates patient and parents in improving glycaemic control. One year after there is worsening of glycaemic control due to lack of patient motivation which implies the need for yearly reeducation.

P2-d1-917 Glucose Metabolism 12

No evidence for heart dysfunction and blood pressure disorders in pubertal children after 5-10 years of type 1 diabetes duration: results of a pilot study

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Background: Cardiovascular disorders, are the main cause of mortality and morbidity in adults with type 1 diabetes (DM1). Nevertheless it is still unclear whether they depend on DM1 duration time, and when the screening for clinically significant abnormalities in asymptomatic adolescents/young adults should start.
Objective and hypotheses: The assessment of the influence of 5-10 years DM1 duration time on heart structure and function, and blood pressure in adolescents.
Methods: In 26 patients (17 girls) with DM1, mean age 12.65 years (SD 0.67) without overt complications of DM1 and hypertension, HbA1c, BNP levels, echocardiographic (M-mode, 2D, classic and tissue Doppler) parameters, blood pressure (24-hour ABPM) were determined. Results were analyzed comparatively in groups with long (5-10 years, n=12, G1) and short (< 5 years, n=14, G2) DM1 duration time.
Results: There were no significant differences in BMI SDS (0.2 vs. 0.12 p=0.98) and HbA1c levels (59 vs. 57 mmol/mol). The mean BNP level was higher, but not significantly in G1 (12.5 vs. 11 pg/ml, p=0.95). There were no significant differences in mean left (LV) and right (RV) ventricle and intraventricular septum systolic (s) and diastolic (d) dimensions (RVd 1.9 vs.2.05; LVd 4.5 vs.4.4; LVs 2.8 vs.2.9; IVSd 0.7 vs.0.67; IVSs 1.02 vs.0.99 cm), and isovolumetric relaxation time (0.065 vs.0.064s), deceleration time (0.12 vs.0.12s), E/A wave ratio (1.77 vs.1.75), E/E' wave ratio (7.88 vs.7.01) and myocardial performance index (0.29 vs.0.3). There were no significant differences in mean arterial, systolic and diastolic blood pressure (81vs.82; 110 vs,112; 66vs. 67 mmHg), night dip (13.78 vs. 9.4%), and heart rate (76,8 vs. 81,4/min). There were no correlation between BNP level, echocardiographic and blood pressure parameters, and DM1 duration time.
Conclusions: There is no evidence for clinically significant heart dysfunction and blood pressure disorders in pubertal children after 5-10 years of DM1 duration time**.**

P2-d1-918 Glucose Metabolism 12

Novel case of insulin resistant diabetes secondary to newly described autoinflammatory disorder: CANDLE syndrome

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Background: Autoinflammatory diseases result from perturbations in innate immune system and cause episodic and systemic inflammation. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE syndrome) is recently described in children and characterized by onset during first year of life, recurrent fevers, erythematous skin lesions, swollen eyelids, panniculitis-induced lipodystrophy, anaemia and failure to thrive. Mutation in the PSMB8 gene cause CANDLE syndrome.
Clinical case: A 10 year old Eurasian girl born to consanguineous parents presented at 2 years of age for pneumonia and anaemia.Further assessment revealed history of urticarial rash since 6 months of age, periodic fever, failure to thrive and hepatosplenomegaly. Investigations showed chronic anaemia, elevated acute phase reactants, raised liver enzymes. Bone marrow was reactive and skin biopsy showed vasculitis with leucocytoclasis.CT scan of

the brain revealed bilateral basal ganglia calcification. Molecular testing confirmed mutation in the PSMB8 gene.
Treatment included prednisolone and cyclosporine (with no improvement), anakinra (interleukin-1 receptor antagonist) with partial control of fever and skin lesions and pulsed methylprednisolone for recurrent flares. In the last 2 years she developed severe lipodystrophy and features of insulin resistance which included hyertriglyceridemia, hyperglycemia & acanthosis.She required high doses of insulin up to 2 units/kg to control her hyperglycaemia. Her terminal events were intrabdominal sepsis, pancreatitis, diabetic ketoacidosis and acute renal failure.
Conclusion: Elucidation of molecular basis for these disorders has lead to improved understanding & treatment. Interferon may be a key mediator of the inflammatory response and present a therapeutic target.PSMB8 encodes the inducible β5i subunit of the proteasome which is critical for maintaining cell homeostasis by removing degraded proteins.

P2-d1-919 Glucose Metabolism 12

Does type 1 diabetes influence lung function? Results of a pneumo-allergological follow-up study

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Background: Type 1 Diabetes Mellitus (T1DM), overweight/obesity and atopy-related disorders like asthma and allergic rhinitis are common chronic diseases with clinical onset in childhood and represent growing health issues, especially in Western Countries. Defining the relationship between these diseases and their influence on lung function is intriguing: poor metabolic control impairs pulmonary function indexes; high BMI is related to decreased respiratory volumes and fluxes. IgE-mediated sensitization to domestic inhalant allergens (e.g. dust mite, cat and dog epithelium) is an important risk factor for asthma.
Objectives and hypotheses: To evaluate longitudinally 43 young T1DM patients with known allergologic background and to analyze the role of metabolic control, insulin requirement and BMI-SDS on the evolution of respiratory function.
Methods: Allergic sensitization tests and spirometry were performed in 43 patients (25 m, 18 f, median age at follow-up 18.4 years, 1st-3rd q: 16.7-20.8). Median HbA1c, insulin requirement and BMI-SDS were evaluated.
Results: At follow-up allergic sensitization was founed in 29 pts (67,4%) as at baseline; 20 pts had allergic rhinitis, while 9 were asymptomatic. Sensitization to dust mites was prevalent at follow-up. An increased sensitization to dog epithelium [0/43 to 14/43 patients (32.6%), P=0.0005] was observed; sensitization to cat epithelium increased [4/43 (9.3%) to 10/43 patients (23.3%)], even if not significantly. An increased sensitization to both epithelia [4/43 (9.3%) to 16/43 (37.2%) pts, P=0.003] was found. No patient had asthma at follow-up. At follow-up a worsening in FVC (P=0.003) and FEV_1 (P=0.001) was found. No correlation was found between HbA1c levels, insulin requirement or BMI-SDS and pulmonary function indexes.
Conclusions: Periodic pneumo-allergological evaluation is recommended in young T1DM pts to identify allergic sensitization that may compromise lung function, even if in absence of symptoms.

P2-d1-920 Glucose Metabolism 12

Non-alcoholic fatty liver disease: a novel risk factor for the development of type 2 diabetes in childhood?

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Background: Non alcoholic fatty liver disease (NAFLD) is associated with obesity, insulin resistance (IR) and increased type 2 diabetes (T2D) risk. The physiopathology of these interactions remains unclear in pediatrics population. Alanine aminotransferase (ALT) is a recognized biochemical marker of NAFLD actually used as screening of this disease.
Objective and hypotheses: To estimate the associations between (ALT) with IR and endothelial inflammation parameters.
Method: 348 subjects (52.7% females) between 4.9 - 15.6 years old were studied. Fasting blood samples was obtained to determinate: ALT, aspartate aminotransferase (AST), glycaemia, insulin, lipid profile, high sensitive PCR (hsPCR), tumoral necrosis factor-α (TNF-α), interleukin-6 (IL-6) and adiponectin (A). HOMA-IR, QUICKI and HOMA-β were calculated. Variables were log10 transformed before Pearson correlations analyze.
Results: ALT levels were positively correlated with BMI-SDS (r= 0.335; P< 0.0001), waist/ height ratio (r= 0.358; P< 0.0001), insulin (r= 0.33; P< 0.0001), HOMA-IR (r= 0.33; P< 0.0001), HOMA-β (r= 0.26; P< 0.0001), TG/HDL-c (r= 0.2; P< 0.0001), hsPCR (r=0.3; P< 0.0001); and inversely correlated with QUICKI (r= -0.25; P< 0.0001) and adiponectin (r= -0.113; P=0.03). No correlation between ALT with: glycaemia (P=0.60), TNF-α (P=0.14) and IL-6 (P=0.82) was found.
Conclusion: Our study demonstrated that ALT was significantly correlated with markers of IR and endothelial inflammation, all of them recognized as risk parameters of pre diabetes stage. Therefore, we suggest the measurement of ALT as a marker of NAFLD should be part of the evaluation of all obesity children, mainly those with other cardiometabolic risk factors, since it could predict later development of T2DM.
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P2-d1-921 Glucose Metabolism 12

Hypoglycaemia rate during diabetic ketoacidosis, managed with the two-bag system

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Introduction: Diabetic ketoacidosis (DKA) accounts for 15% of diabetes-related hospitalizations. Hypoglycemia is the most common complication during DKA management. The two-bag system consists of 2 fluid bags of different dextrose concentrations tri-fused with insulin, allowing for rapid dextrose titration to prevent hypoglycemia, while insulin is infused until ketone clearance.
Objective and hypothesis: Examine the rate and degree of hypoglycemia in DKA patients in the pre-implementation (pre-I) and post-implementation (post-I) era of a standardized two-bag system protocol.
Methods: This retrospective chart review included 381 DKA patients > 1 year old presenting to Seattle Children's Hospital, 188 pre-I and 193 post-I. Hypoglycemia was defined as a serum glucose ≤ 70mg/dl during treatment of DKA. Comparisons and correlations were performed.
Results: A total of 30 subjects developed hypoglycemia, 13 (43%) of which had multiple events. The majority were Caucasian (n=20, 67%) and males (n=19, 63%). Mean age was 9.8 ±5.1 years and mean serum glucose was 60.4±9.3 mg/dl. Half (n=15) had known T1DM. There was a weak positive correlation between degree of hypoglycemia and age (r=0.25), but no correlation with BMI z-score or presenting pH. Hypoglycemia rate did not differ by

gender or race. Equal numbers developed hypoglycemia in each of the pre and post-I groups (8.3% vs.7.7%, p=1.0). In the post-I era, 9/15 subjects (60%) developed hypoglycemia events due to failure to transition to subcutaneous insulin, albeit ketone clearance (beta-hydroxybutyrate < 1mmol/L). Post-hoc analysis comparing rate of hypoglycemia in both pre and post-I groups, after exclusion of these 9 patients, was significant (p=0.04).
Conclusions: The majority of hypoglycemia events during DKA management would have been prevented if the standardized two-bag system protocol was followed, with timely transition off the insulin drip.

P2-d1-922 Glucose Metabolism 12

Epidemiology of childhood type 1 diabetes in Extremadura (1996-2011)

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Background: The rising incidence of Type 1 diabetes (T1DM) globally suggests the need for continuous monitoring of incidence. There is wide geographical variation, even between different regions of the same country.
Objectives:
- To estimate the incidence of T1DM among the children's population in Extremadura (1.108.130 inhabitants) from 1996-2011 and to find out general epidemiological characteristics.
- To analyze the association with autoimmune diseases and related family history.
Methods: Retrospective study of population under 13 years old and T1DM in Extremadura from 1996-2011. The information was collected from a primary source, hospitals, and secondary sources, diabetic camps and associations.
Results: 577 children were diagnosed. Completeness of registration was 98,9%. The age-adjusted incidence: 22,7cases/100.000, highlighting the group of girls from 10 to 13 years old (30,5/100.000). It is not appreciated annual increase progressively. There were 56.3%girls and 43,7%boys. The mean age at the onset of T1DM was 7.5 years. Seasonal pattern: fall 29,9%, winter 25,3%, summer 23,4% and spring 21,4%. 60,2% live in rural areas. 22% of cases presented a family history of DM1 and in 12.16% other autoimmune diseases. 17,2% of patients had associated autoimmune diseases (thyroid disease: 10,2% and coeliac disease: 5,2%). 21,5% of patients presented ketoacidosis diabetic (KAD) at the onset of T1DM, most commonly in the 0-4 years old group(38.6%). In 6,9% of cases, symptoms were not reported previously.
Conclusions:
1. The estimated incidence of T1DM in Extremadura belongs to the group of "very high incidence" (WHO project DiaMond), one of the highest in Spain. There has not been a steady increase year on year in the annual incidence of this disease in this region. It seems there is a period of stabilization. The estimated incidence is higher in girls than in boys.
2. There is other autoimmune diseases in the family history (12%) more often than in the rest of the population.

P2-d1-923 Glucose Metabolism 12

The role of diabetic ketoacidosis in the evolution of type 1 diabetes in children

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Background: Diabetic ketoacidosis (DKA) represents the most frequent metabolic complication which requires hospitalization of the child with type 1 diabetes mellitus (DM).
Objective and hypotheses: Evaluation of the impact of DKA in the evolution of type 1 DM.
Methods: The study included 56 children newly diagnosed with type 1 DM, aged between 2 and 18 years. In these cases we evaluated: clinical features, the frequency and severity of DKA, factors that influenced the DKA.
Results: Clinical features: predominance of female cases (60.7%) and cases from urban areas (55.3%).
Studying the age distribution of cases we have found that age group 6-12 years was the most common (58.9%), followed by age group 2-5 years with a rate of 22.7% and 13-18 years with 18,4%. DKA incidence was 96.4% (54 cases), moderate form of DKA was predominant in 30 cases (53.5%), mild in 17 cases (30.3%) and severe in 7 cases (12.5%).
The most frequent causing factors of DKA were the early age of diabetes onset, between 2 - 6 years (80,5%) and respiratory infections (62,1%). The incidence of partial remission period was 44.6%. At the cases with partial remission, the incidence of DKA was 92% (23 cases), mild DKA was present in 13 cases (52%) and moderate form in 10 cases (40%).
We have tried to correlate the incidence of remission period with clinical form of ketoacidosis and we have found that from 17 cases with mild DKA, 11 cases (64,7%) entered remission. From 30 cases with moderate DKA only 10 cases (33,3%) entered remission and none of the cases with severe DKA at onset presented any remission.
Comparing the two subgroups, we have found that DKA at onset correlates with a lower incidence of the remission period ($p < 0.001$).
Conclusions: The degree of metabolic decompensation at the onset of the diabetes represents an important factor that influences the occurrence and duration of remission.

P2-d1-924 Glucose Metabolism 12

Novel fructose-1,6-biphosphatase gene mutation in two siblings

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Background: Fructose-1,6-biphosphatase (FBP) deficiency is an autosomal recessively inherited disease, which progresses with severe hypoglycemia and metabolic attacks; and is caused by a defect in gluconeogenesis. If not appropriately treated and fructose is not excluded from the diet, it may have a fatal outcome.
Case reports: Two-year old girl was referred to our clinic because of lactic acidosis, uncorrectable hypoglycemia, and increased transaminases. FBP deficiency was suspected in the patient as the case recovered dramatically after high dose glucose infusion and adequate bicarbonate replacement. There was first degree consanguinity between the parents. Three-year old male sibling of the patient was also hospitalized twice because of hypoglycemic attacks and metabolic acidosis. Different from the previous analyses, homozygote c.658 del T mutation was detected at the 5th exon of FBP1 gene in those two siblings.
Conclusion: We indicated in our study that this mutation, which was defined for the first time and was presented for the first time in our country, was a disease triggering factor.

P2-d1-925 Glucose Metabolism 12

Improving paediatric diabetic ketoacidosis: lessons from a multidisciplinary quality improvement initiative in the computerized era of medicine

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Objective: We report on the successful development, implementation and sustained improvement of an evidence based pathway for the hospital management of diabetic ketoacidosis (DKA).
Methods: Development of the pathway involved the systematic synthesis of published literature by a multidisciplinary team. Implementation included multidisciplinary feedback and hospital wide education, computer decision supports and daily team huddles. Initially computerized, pathway based order sets forced clinical pathway compliance, yet, variations in care persisted, requiring ongoing review and pathway tool adjustment. Quality improvement measures have identified barriers to improvements and informed subsequent adjustments to interventions. The most notable - First, careful attention to potassium levels identified clinically significant hypokalemia not recognized prior to implementation, with only marginal improvements seen afterwards; earlier addition of potassium to initial fluid replacement has provided notable improvements. Second, delays in the ordering of, as well as transitioning patients off, insulin infusions have been addressed in a standardized fashion within the order set; optimal insulin drip initiation and termination reduced lead time and potential worsening of DKA severity and iatrogenic hypoglycemia respectively.
Results: Since implementation we have included over 200 patients on the pathway. We continue to convene quarterly meetings, review cases, and process ongoing issues with system based elements of implementing the recommendations.
Conclusions: Our development and implementation of a successful evidence based pathway for DKA has lead to overall improvements in care and recognition of areas for future work. Such direction include addressing management of patients with ketosis but not frank acidosis and the importance of community outreach and education regarding DKA management recommendations. Full pathway available at: http://child.childrens.sea.kids

P2-d2-926 Glucose Metabolism 13

Permanent neonatal diabetes mellitus caused by a novel mutation in KCNJ11 gene

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Introduction: Mutations in the KCNJ11gene are responsible for the majority of permanent neonatal diabetes mellitus (PNDM). Some mutations including p.Q52R in this gene are associated with DEND (developmental delay, epilepsy, neonatal diabetes) syndrome. In this report, we present a case of PNDM caused by a novel heterozygous missense mutation p.Q52L in the KCNJ11.
Case study: A 22 day old girl was referred with a history of vomiting and hyperglycemia (752 mg/dl). The patient was born at 39 gestational weeks by vaginal delivery after unremarkable pregnancy. Her birth was 2200 gr (< 10th percentile). Physical examination findings were unremarkable except for irritability. Laboratory studies revealed hyperglycemia (516 mg/dl), glucosuria (+4) and trace ketonuria.
Other laboratory and radiological studies were unremarkable. Hyperglycemia persisted after a regular insuline dose. The patient was diagnosed as having diabetes mellitus and started subcutaneous insulin. At age 6 months the infant was succesfully transfered from insulin to sulphonylurea. A novel heterozygous missense mutation p. Q52L (c.155A>T) in the KCNJ11 gene was found. This patient doesn't have any neurological finding although she has a mutation in the same residue of KCNJ11 for the previously reported cases.
Conclusions: This report suggests that Q52 mutation in the KCNJ11 does not always lead to DEND syndrome.

P2-d2-927 Glucose Metabolism 13

A survey of monogenic diabetes forms in Switzerland

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Background: Monogenic diabetes (MD) are due to single gene defects affecting beta-cell development or function, thereby disturbing insulin secretion. They result in neonatal diabetes or in diabetes diagnosed in young adults and also referred to as maturity onset diabetes of the young. MD affect 2-5% of all diabetic patients. In Switzerland, this represents an estimated population of 10'000 - 25'000 patients, most of which are probably diagnosed and treated as type 1 or type 2 diabetes.
Objective and hypotheses: Recognizing MD is important for patients, since the diagnosis will determine treatment modalities and allow for a more precise estimate of the risk for long-term complications. We have performed a survey to assess the number of suspected and diagnosed cases in Switzerland. We now also offer genetic analysis for all genes implicated in known monogenic diabetes forms.
Methods: A questionnaire was sent to all members of the Swiss Society of Endocrinology and Diabetology to determine the number of diagnosed or suspected cases of monogenic diabetes in Switzerland as well as to gather information on clinical parameters and current treatment. Genetic analysis of monogenic diabetes is performed by HaloPlex technology allowing sequencing of amplified target DNA. Candidate genes found by this technology are then sequenced.
Results: So far, 68 subjects with MD were reported. The diagnosis was genetically proven in 52% of the suspected cases. Mutations in the *glucokinase (GCK)* gene was found in most cases, followed by mutations in *HNF1b, HNF1a, HNF4a and KCNJ11*. The distribution was similar in adult and pediatric patients.
Conclusions: We are currently sequencing all the clinically suspected monogenic diabetes forms in Switzerland and offer genetic diagnosis for all known monogenic diabetes genes. First results indicate that mutations in *GCK* are most frequently found in suspected cases.

P2-d2-928 Glucose Metabolism 13

Management of Rabson-Mendenhall syndrome

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Introduction: Rabson-Mendenhall is a rare syndrome associated with severe insulin resistance. In this report it was presented a patient with Rabson-Mendenhall syndrome who developed diabetic ketoacidosis (DKA), the clinical course of this acute complication and maintenance therapy after recovery of ketoacidosis.
Case study: A girl diagnosed as Rabson Mendenhall syndrome at the age of 3, was admitted to the hospital with severe DKA when she was 9 year and 4 month old. At the end of the third day of ketoacidosis management, the clinical and laboratory improvement were obtained. Despite the high insulin maintenance doses, metformine and thiazolidinedione therapy, hyperglycemia and poor metabolic control were not able to be improved; therefore, insulin like growth factor-1(IGF-1) therapy was given at a dose of 120 mcg/kg twice daily but this additional therapy was also not effective to improve metabolic control.
Conclusions: The treatment of diabetic ketoacidosis in children with severe insulin resistance must be individualized. For an efficient treatment, insulin

infusion should be started with higher doses than proposed procedures for type 1 diabetes mellitus. Improvement in metabolic control could not be obtained with IGF-1 therapy at a dose of 120 mcg/kg twice daily in all children with Rabson-Mendenhall Syndrome.

P2-d2-929 Glucose Metabolism 13

A novel type heterozygous mutation in the glucose-6-phosphatase gene in a patient with glycogen storage disease Ia

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Background: The catalytic subunit of microsomal glucose-6-phosphatase (G6Pase; G6PC, GenBank accession number: U01120) is a key enzyme involving the terminal step in gluconeogenesis and glycogenolysis, which is primarily expressed in the liver, kidney and intestinal mucosa. Glycogen storage disease type Ia (von Gierke disease or GSDIa, MIM ID: 232200) is an autosomal recessive disorder caused by deficiency of G6Pase. Since the cloning of the gene coding for G6Pase, more than 89 mutations(Human Gene Mutation Database; http://www.hgmd.cf.ac.uk) have been identified in different ethnic groups. But, there are still some patients with GSDIa can't be diagnosed because of novel type mutation. These patients and their family members would suffer from agony and perplexity.
Objective and hypotheses: By genotype analysis of the affected pedigree, we identified a novel type mutation in a patient with GSD Ia.
Methods: Mutation analysis was performed for the coding region of G6Pase gene using DNA sequencing and TaqMan gene expression assay was used to further confirm the novel mutation.
Results: The proband was compound heterozygous for c.311A>T/c.648G>T.
Conclusions: Interestingly, the mutation reported by us is extremely rare. The case presented here has proved that there is a low risk of chronic liver complication before a mild GSDIa patient's second decade of life, even without any dietary therapy. In mild GSDIa patients, the risks and benefits of organ transplantation or future gene therapy should be seriously considered. However, the long-term complications including hepatic adenoma or hepatocellular carcinoma of this patient must be monitored in the future.

P2-d2-930 Glucose Metabolism 13

Achievement of internationally established metabolic goals in Spanish paediatric patients with type 1 diabetes

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Background: The "T1D Exchange Clinic Registry" of 13.316 pediatric patients with type 1 diabetes (T1D) (2013) in U.S. recently revealed that most children have HbA1c values above target levels established by the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD).
Objective and hypotheses: To assess the proportion of youngsters with T1D who meet the internationally accepted targets for good metabolic control of diabetes at a single, referral Pediatric Diabetes Center in Spain.
Methods: Cross-sectional study of 247 children and adolescents with T1D controlled at our Pediatric Diabetes Unit. We analyzed the compliance to metabolic goals set by ADA (HbA1c: < 6 years: < 8.5%, 6-12 years: < 8% and 13 to 18 years: < 7.5%, LDL< 100mg/dl, BP< p95th for age, sex and height and BMI< p85) and ISPAD (HbA1c < 7.5% for all ages; LDL < 100mg/dl and BP < p90th), and analysedcompliance differences between patients treated with continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI). Statistics: SPSS™ version 17.0.
Results: T1D patients (47% women, mean age 12.6±4.6 years, T1D duration 6.4±4.3 years) had mean HbA1c levels of 6.9±0.69%. ADA/ISPAD HbA1c targets were achieved by 100/100% of patients < 6 years, 100/91% of children 6-12 years and 88/85% of 13-18 year old teens. Table 1.

Patients	Total n=247	CSII n=69 (28%)	MDI n=178 (72%)	p
Mean HbA1c < 6 years	6.9±0.69%	6.4±0.12%	6.97±0.23%	0.0035
Mean HbA1c 6-13 years	6.78±0.28%	6.7±0.49%	6.78±0.55%	1
Mean HbA1c 13-18 years	7±0.8%	6.74±0.5%	7.05±0.85%	0.06
HbA1c ADA targets	93%	98%	90%	0.56
HbA1c ISPAD targets	89%	91%	88%	0.51
LDLc<100mg/dl	53%	40%	57%	0.03
BP<p95th	100%	100%	100%	0.9
BP<p90th	99%	100%	99%	0.9
BMI<p85th	91%	91%	91%	0.94

[Table 1]

Conclusions: Most patients in our children and adolescent cohort of T1D patients correctly achieve metabolic goals established by ADA and ISPAD irrespective of the therapeutic modality.

P2-d2-931 Glucose Metabolism 13

A screening test for the cause of hypoglycaemia is a valuable tool for identification of the underlying diagnosis

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Background: A battery of tests is usually performed to help identify the cause for hypoglycaemia (defined as an estimated laboratory plasma glucose < 2.7 mmol/l) once it is suspected on near patient testing. It usually involves confirmation of hypoglycaemia with an estimated laboratory plasma glucose and concurrent samples examined for plasma lactate, insulin, C peptide, β hydroxybutyrate, free fatty acids, growth hormone, cortisol, free carnitine, amino acids, blood spot acyl carnitine and urine organic acids. Further investigations are undertaken depending on the results and any further clinical pointers. This is labour intensive. There is little published data on its value.
Objective: Assess the usefulness of screening tests in determining the underlying cause for hypoglycaemia.
Method: All completed hypoglycaemia screening tests undertaken at a tertiary referral centre for congenital hyperinsulinism between 2009 and 2012 were assessed retrospectively to identify the outcome. Patients with hypoglycaemia with clinical features suggesting the underlying diagnosis who did not have screening tests were excluded from this study.
Results: There were 160 sets of screening tests obtained from 92 patients (51 males) median age (range) 3 months (1 day - 20.5 years) suspected to have hypoglycaemia. Only 60 sets from 41 patients median age (range) 16 months (1day - 14.7 yrs) confirmed hypoglycaemia. See table below.

Diagnoses	Blood test sets	Number of patients identified
Hyperinsulinism	27	23
Peroxisomal Disorder1	1	1
MPV17 mutation	4	1
Growth Hormone Deficiency	1	1 (with other clinical features)
Idiopathic	27	15

[Diagnoses following hypoglycaemia screen]

Twenty six out of 41 patients (63%) had their diagnosis identified as a result of the screening tests.
Conclusion: Screening tests for hypoglycaemia is highly useful in identifying the underlying cause for hypoglycaemia in a tertiary endocrine referral centre for hyperinsulinism.

P2-d2-932 Glucose Metabolism 13

Identification of a novel mutation in an Egyptian infant with microcephaly, epilepsy, and permanent neonatal diabetes (MEDS) syndrome

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Introduction: A recently delineated microcephaly with simplified gyration, epilepsy, and permanent neonatal diabetes syndrome (MEDS) was identified.
Case study: Here we describe an Egyptian female infant (deceased) fourth order of birth born to consanguineous healthy parents. The pregnancy was uneventful and she was delivered at term vaginally. At 2 months of age she presented with severe hyperglycemia and was diagnosed as infantile diabetes. On examination, she had microcephaly greater than -2.5 SD below the mean, developmental delay, hypotonia, epilepsy. Later, the seizures were a combination of focal seizures with secondary generalization and generalized seizures. EEG showed polyspikes and slow waves with burst suppression pattern. Brain MRI revealed microcephaly with simplified gyration, cortical atrophy, hypoplastic corpus callosum and delayed myelination. The diabetes and epilepsy were difficult to control despite treatment with clonazepam, vigabatrin, and sodium valproate and patient continued to have repeated pneumonias. No neurodevelopmental progress was noticed and she required intervention via nasogastric tube. No skeletal defects, liver or renal dysfunction were reported. Patient died at the age of 10 months of severe pneumonia complicated by therapy-resistant epilepsy and diabetes. In the family, one more sibling died reported as having respiratory distress, but neither clinical data nor genetic screening were available. The parents also have a healthy daughter and son. Genetic analysis identified a homozygous missense mutation of the immediate early response 3 interacting protein 1[IER3IP1] gene (exon 3 p.L78P c.233T>C) and parents are both heterozygous for this mutation.
Conclusion: This gene mutation mostly leads to apoptosis of neurons and pancreatic beta cells in patients implicating mechanisms of brain development and on the pathogenesis of infantile epilepsy and early-onset permanent diabetes.

P2-d2-933 Glucose Metabolism 13

Frequency of glutamic acid dehydrogenase antibodies among paediatric Filipino with type 1 diabetes mellitus

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Background: GADA (glutamic aicd dehydrogenase antibody) is an important marker for human autoimmunity of Type 1 diabetes mellitus (DM1), with frequency that varies depending on the population and the duration of the disease.
Objective and hypotheses: The aim of the study was to determine the frequency of GADA and its association with age, sex, BMI, age at diagnosis, duration of the disease and family history of diabetes among pediatric Filipino DM1.
Methods: A hospital based cross sectional study was conducted among DM1 pediatric patients attending at the diabetic clinic in a tertiary hospital. The GADAs were detected with commercial immunoradiometric assays.
Results: A total of 68 pediatric diabetic patients participated in the study of whom 40 (58.8%) male and 28 (41.2%) female. The prevalence of GADA in the study population was 30/68 (44.12%). There was no significant association in age, sex, BMI, > 2 years duration of diabetes and GADA. The age of onset (P=0.01), < 2 years of disease duration (P=0.01) and family history of diabetes (P=0.03) were significantly associated with GADA.
Conclusions: The frequency of GADA in pediatric Filipino DM1 is comparable to other Asian populations. Levels of GADA are strongly influenced by age at diagnosis and recent onset of DM1 (< 2 years).

P2-d2-934 Glucose Metabolism 13

A new case of exercise-induced hyperinsulinism caused by MCT1-expressing insulinoma

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Background: Exercise-induced hyperinsulinism (EIHI) is a rare hypoglycaemic disorder characterized by inappropriate insulin secretion following anaerobic exercise. Activating mutations within the monocarboxylate transporter 1 promotor (MCT1) have previously been described as a possible cause of EIHI resulting in inadequate expression of MCT1 in beta cells. However, to date, MCT1 expression has not been demonstrated in insulin-producing cells from EIHI patients.
Patient: A 16 year-old male patient with recurrent episodes of drowsiness or syncope was diagnosed with hyperinsulinaemic hypoglycaemia. During spontaneous hypoglycaemia (2.3 mmol/l) serum insulin was elevated (576 pmol/l). Diazoxide was started but control of hypoglycaemia was not satisfying and the patient was further evaluated at our institution.
Methods: Insulin secretion was studied during an anaerobic exercise test before and after resection of an insulinoma. The expression of MCT1 was studied by immunohistochemistry, real-time RT-PCR and western blot analysis. The presence of MCT1 protein was analysed in four additional insulinoma patients.
Results: Preoperatively, but not postoperatively, anaerobic exercise resulted in massive insulin secretion and severe hypogycaemia consistent with EIHI. Sonography and MRI revealed a focal region within the head of the pancreas. The tumor was enucleated and histology confirmed insulinoma. Subsequent analysis revealed MCT1 expression in the insulinoma tissue but not in the patients' normal islets. Postoperatively, the patients' blood glucose is stable without any medication. MCT1 protein was detected in three of four additional insulinomas.
Conclusion: We recommend an anaerobic exercise-test in all patients with unknown cause of hyperinsulinaemic hypoglycaemia, especially when symptoms are related to physical exercise. Our data suggest that MCT1 expression in human insulin producing cells can lead to EIHI and that MCT1 might be present in most insulinomas.

P2-d2-935 Glucose Metabolism 13

Development and implementation of clinical practice guidelines in diabetic ketoacidosis: NICE is also nice in the Middle East

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Background: Clinical Practice Guidelines (CPG) are tools to assist practitioner and patient taking evidence based decision. CPGs assist in delivering a high quality service.
Objective and hypotheses: We aim to review our experience in synthesis and implementation of CPG in our Pediatric Endocrinology Unit taking Diabetic ketoacidosis (DKA) as an example to highlight the challenges and outcome of CPG.
Methods: A departmental steering committee selected CPG topics based on high risk high volume, according to the recent patient census. DKA was selected as a priority topic. We used Resource Toolkit developed by ADAPTE collaboration (International Collaboration of guideline Developer) for development of CPG. CPGs were selected and appraised according to AGREE format (Appraisal of Guidelines for Research and Evaluation) to evaluate the

strength of recommendations and the quality of evidence. Four existing CPGs on DKA were appraised. National Institute for Clinical Excellence (NICE) guidelines for management of DKA was selected scoring high on the list. Minor changes done to suit our setting. All stakeholders including endocrinologists, intensivists, emergency physicians, nurses and dieticians were involved. An audit was conducted after two years of implementation of CPG for DKA.
Results showed that CPG enhanced the quality of care and improved patient outcome. It reduced variations in practice. Adherence to CPG was good. Pediatric intensive care stay was significantly reduced and no mortality reported. Challenges observed include convincing doctors to adhere to CPG that was fixed by continuing education of doctors. Commitment and motivation of staff was crucial for success of CPG.
Conclusions: This paper highlights the process of development and implementation of CPG and reports the challenges, outcome and impact on service.

P2-d2-936 Glucose Metabolism 13

Assessing service satisfaction levels of adolescents with diabetes in out-patient clinic setting: a patient response outcome measure

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Background: Managing services is an important component of medical leadership competency framework in the NHS. Service users' feedback and experiences are key issues that impact on service delivery. The 'You Are Welcome' quality criteria, best practice guidance from Department of Health, recommends involving young person in monitoring and evaluation.
Objective: To evaluate service provision and assess needs of adolescents with diabetes.
Methods: A survey questionnaire (with free text option) was provided to all adolescents attending the diabetic clinic and transition clinic over a 3 month period. Respondents submitted the questionnaire to the diabetic team which then in-putted the data onto an on line survey form. Responses were collated by the Patient Experience Unit and examined.
Results: Total 22 adolescents (12 males, 10 females) participated. 95% rated the service >7/10 while 36% rated the service 10/10. 86% were able to describe their condition, 14% were unsure. Majority could differentiate hypo / hyper glycemia episodes and were aware of long term complications of diabetes. Knowledge about sexual health was poor. There was poor awareness of web-sites relating to diabetes. Upto 70% families had parking problems during clinic visits.
Conclusions: Overall satisfaction regarding diabetes service provision was good. Patients preferred to see the same medical professional at subsequent visits. Adolescents also preferred attending clinics later during the day. Satisfaction surveys contribute to critically evaluate service provision and improve quality in healthcare. **HEADSS (H**ome and environment, **E**ducation, **A**ctivities, **D**rugs, **S**exuality, **S**uicide and depression) questionnaire can be useful tool during clinic consultation with young people.
Services need to be made more young people friendly to enable better outcomes in adolescents with diabetes.

P2-d2-937 Glucose Metabolism 13

Efficacy analysis of MDI or CSII in type 1 diabetes mellitus children of different duration

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Background: DCCT has already proved that intensive therapy is better than conventional treatment for diabetes. But many other researches about intensive treatment got controversial results.
Objective and hypotheses: We assessed the effect of MDI/CSII treatment for T1DM children in different durations.
Methods: Real world research, retrospective analysis design. We got 252 T1DM children from 935 cases in 2001-2012. Patients who switched to applying MDI/CSII in the course of within 1 year and 1-3 years respectively and set to group 1A and group 2A. Matched control patients were treated by insulin 2 injections per day (group 1B and group 2B). We compared HbA1c, insulin dose, BMI, SMBG frequency and poor control rate during the observation period (baseline-3m-6m-12m-24/36m: V0-V4). Logistic regression analysis was used.
Results: HbA1c of group 1A during observation period (24-36 months) was lower than that of group 1B (V1: 7.35 vs. 7.89, V2: 7.37 vs. 8.21, V3: 7.61 vs. 8.41, V4: 7.61 vs. 8.72, $P < 0.05$). Insulin dosage of group 1A from baseline to 12 months was higher than that of group 1B (V0: 0.59 vs. 0.39, V1: 0.54 vs. 0.41, V2: 0.58 vs. 0.47, V3: 0.68 vs. 0.57, $P < 0.05$). HbA1c of group 2A in 6 months was lower than that of group 2B ($P < 0.05$). Logistic Regression analysis showed that HbA1c is related positively to boy, insulin dose and BMI (P is 0.04, 0.002 and 0.038 respectively).
Conclusions: Applying MDI / CSII therapy, both of them, early or late, can improve HbA1c. The Early group can keep HbA1c at a low level persistently in 2-3 years. While the later only get lower HbA1c in a very short term. Logistic Regression analysis reveal good glycemic control was not by MDI or CSII methodology, and we should pay more attention to boys, adjust insulin dose in time, and control BMI strictly.

P2-d3-938 Glucose Metabolism 14

Ketoacidosis related to alcohol consumption but not to type 1 diabetes in an adolescent with type 1 diabetes

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Background: Alcohol consumption might result in ketoacidosis by inhibiting gluconeogenesis which then results in an energy crisis and lactic acidosis.
Case report: A 12-year old adolescent girl with known diabetes type 1 and on insulin treatment since 5 years was referred to a private hospital in Istanbul with the preliminary diagnosis of Reye syndrome for liver transplantation from an Eastern European country.
As her alcohol consumption, which was later discovered, was unknown to her parents, thus to physicians, in her country, all efforts were directed to the treatment of presumed diabetic ketoacidosis and later presumed Reye syndrome. Initial complaints and symptoms were not feeling well, vomiting, chest pain and confusion followed by gastrointestinal bleeding,ketoacidosis, hyperglycemia then by coma, respiratory failure, renal dysfunction, hepatosteatosis and brain edema.Reye syndrome was considered as a possible diagnosis.
When in Istanbul, she was unconscious. She was immediately taken to the ICU and supportive treatment together with appropriate insulin treatment was started. She had respiratory acidosis, hyperglycemia, renal insufficiency, hypokalemia and hypophosphatemia. Liver function tests and blood ammonia level was normal. Cranial CT was normal. Thus, Reye syndrome was excluded. Respiratory acidosis, hypokalemia and hypophosphatemia were corrected. The presence of a disparity between blood sugar levels and acidosis, and determination of lactic acidosis from time to time were remarkable during follow up. On the third day, sedative-hypnotic agents were stopped and the patient when conscious stated that she had ingested alcohol (Martini) on the occasion of her birthday.
Conclusion: In this case, the presence of diabetes type1 was a confounding factor which resulted in misunderstanding of the clinical situation and poor management of alcoholic ketoacidosis.Alcohol consumption should be considered a possibility in adolescents with type 1 diabetes and ketoacidosis.

P2-d3-939 Glucose Metabolism 14

Neonatal diabetes mellitus in Vietnam: clinical features and outcome

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Background: Neonatal diabetes mellitus (NDM) is a rare but potentially devastating metabolic disorder characterized by hyperglycemia combined with low levels of insulin. Two main groups have been recognized on clinical grounds, transient NDM (TNDM) and permanent NDM (PNDM).
Objective and hypotheses: To describle clinical features, laboratory manifestations of patient with NDM and evaluate outcome of management.
Methods: Clinical features, biochemical finding, mutation analysis and management outcome of 16 cases were study. All exon of KCNJ11, ABCC8 and INS genes were amplified from genomic DNA and directly sequenced and methylation - specific PCR was detected the loss of methylated region on chromosome 6q24. Patients with ABCC8/KCNJ11 will transfer to sulfonylurea from insulin.
Results: 16 cases (9 girls and 7 boys) onset at 60.75 ± 52.7 days of age with gestation age of 39 ± 1.8 weeks and birth weight of 2620 ± 528 grams. 7/16 cases admitted with polydipsia, polyuria and 9/16 cases with diabetes keton acidosis with pH of 7.12 ± 0.2, HCO_3^- 10.17 ± 9.4 mmol/l, BE -8.5 ± 18.4 mmol/l (-4.9 ÷ -28), blood glucose 34.8 ± 9.8 mmol/l, HbA1C 7.7 ± 2.9 %. Mutation analysis showed 6 cases have heterozygous for a KCNJ11 missense mutation, 5 patients with ABCC8 mutations, 3 patients have abnormal of chromosom 6; 2 patients with INS mutation. The patients have duration of 35.2 ± 37.2 months (0.5 - 132). Three patients with TNDM stop insulin at 9.8 ± 7.1 months of diagnosis. Now all cases have normoglycemic, one patient has mild development delay and two patients have normal development. 13 patients with PNDM: 7 cases successfully transferred to sulfonylureas and did not need insulin injections, 6 cases require insulin, 2/13 cases with DEND syndrome, 11/13 cases have normal development.
Conclusions: It is important to perform screening gene mutation for patients with diabetes before 6 months of age to control blood glucose and follow up the patients.

P2-d3-940 Glucose Metabolism 14

Inflammatory cytokines and the adipokines visfatin, apelin, adiponectin are not upregulated in children with type 1 diabetes without complications

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Background: Inflammation plays a crucial role in macro and microvascular complications and type1 diabetes mellitus (T1DM) patients are at increased risk for such complications. Inflammatory cytokines like Interleukin 6 (IL-6) and CRP were shown to be increased in T1DM and are associated with microvascular complications and atherosclerosis. Increased Tumor Necrosis Factor (TNF-α) levels have also been associated with progressing retinopathy. Visfatin has been shown to be associated with increased intima-media thickness in T2DM.
Objective and hypotheses: We studied if inflammatory parameters are increased in T1DM children and explored the potential alterations of adipokines.
Methods: In a crossectional study we measured in 26 T1DM patients and 31 matched controls the inflammatory cytokines IL-6, TNF-α, the anti-inflammatory cytokine IL-1ra and the adipokines Visfatin, Apelin, Adiponectin. HsCRP, HbA1c, duration of diabetes, BMI and age at diagnosis were also recorded.
Results: In the T1DM group mean HbA1c was 8.3%, mean duration of diabetes 5.62 years and mean age at diagnosis 6.0 years.
Table1: mean values for age, BMI, hsCRP, IL-6, IL1-ra and adipokines in both groups.

Groups	Age (Years)	BMI (kg/m2)	hsCRP (mg/l)	IL-6 (pg/ml)	IL1-ra (pg/ml)	TNF-α (pg/ml)	Visfatin (ng/ml)	Apelin (ng/ml)	Adiponectin (µg/ml)
T1DM	11.6	18.2	2.15	1.57	1006.74	11.61	23.71	1.43	14.64
Controls	11.3	17.5	2.03	1.90	1066.11	9.76	14.83	1.46	13.60
P-value			0.85	0.59	0.75	0.15	0.15	0.87	0.87

[Table 1]

Significance $p < 0.05$
Conclusions: In our study the children with T1DM showed similar levels of cytokines-adipokines as control subjects. However the slight increase of TNF-α and Visfatin in the diabetic group could indicate an increased risk for developing retinopathy and macrovascular complications, respectively. Larger longitudinal studies are needed to evaluate the correlation between these cytokines-adipokines and vascular complications to validate TNF-α and Visfatin as predictive biomarkers in diabetic children.

P2-d3-941 Glucose Metabolism 14

Ovarian dysgerminoma associated with diabetes mellitus

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Case report: A 12 year old girl presented to the children's emergency with polyuria, polydipsia and loss of weight and was subsequently diagnosed with diabetes mellitus. Glutamic acid decarboxylase (GAD) auto-antibodies and anti-Islet cell antibodies were absent. During the same admission, a suprapubic mass was incidentally palpated and she was found to have ovarian dysgerminoma. While she was being treated for diabetes mellitus, she also received treatment for her ovarian tumour. Prior to the surgery, her serum ß-HCG was markedly elevated. With the treatment of her ovarian tumour with surgery and chemotherapy, and normalization of the serum ß-HCG, her insulin requirement was very much reduced. She did not need insulin therapy 2 months after her surgery. Metformin was started after discontinuation of insulin as the impression was that of Type 2 Diabetes Mellitus. This is an unusual case of diabetes mellitus and ovarian dysgerminoma presenting concurrently. The ovarian dysgerminoma appeared to have accelerated the presentation of severe diabetes. We hypothesized that the elevated ß-HCG and possibly other placental hormones from the germ cell tumor caused her to develop insulin resistance and inadequate beta cell insulin secretory response, not unlike the postulated mechanism behind gestational diabetes mellitus. We believe that this is the first report of an ovarian dysgerminoma related diabetes mellitus. Our observation of the temporal relationship in the improvement of diabetes with the removal of the tumour is supportive that the dysgerminoma likely accelerates the presentation of diabetes mellitus in a predisposed individual. Treating the tumour is the key to controlling the diabetes.

Glucose Metabolism 14

Effective treatment with metformin of a teenager with MODY3 and oligomenorrhoea: case presentation

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Background: Maturity-onset diabetes of the young type 3 (MODY3) is after MODY2 next most common cause of MODY in pediatric population. Sulphonyloureas are treatment of choice for MODY3 young patients with excellent results. There are some data support a beneficial effect of metformin in improving ovarian function in adolescents.

Objective and hypotheses: Presentation of teenager with MODY 3 diabetes and oligomenorhoea treated successful with metformin.
Methods: Fifteen and a half year-old girl entered to the general physician because of oligomenorrhoea. In basic biochemical tests glucosuria and blood glucose (BG) 267 mg/dl were detected, so she was referred to a pediatric endocrinologist. She did not present with typical diabetes mellitus (DM) symptoms, but her family history was positive for DM with typical complications treated since diagnosis with insulin in three generations. She was in a good clinical condition, underweight and discrete signs of hyperandrogenism were observed in physical examination. Glucosuria, ketonuria, BG above 200 mg/dl in 24-h BG profile, and HbA1c 7.1% confirmed DM diagnosis and insulinotherapy was administrated. Further diagnostic revealed high levels of C-peptide > 3,0 ng/ml and negative diabetes autoantibodies. Because of low daily requirement of insulin - 0.4 IU/kg and oligomenhorea a decision of the replacement of insulinotherapy with metformin was made.
Results: Three months after metformin introducing HbA1c level normalized and menstruation cycles became to be regular. Genetic tests confirmed MODY3 in the patient and her family. No pathology in the morphology and function of kidneys was found. Because of positive effect on regulation of menstrual cycles and still high C-peptide level, the treatment with metformin has been continued. In last two-years follow-up HbA1c has been varied between 5.6-5.8%, menstrual cycles have been regular.
Conclusions: Metformin could be adequate treatment for teenagers with MODY 3 and oligomenorhea/PCOS.

P2-d3-943 Glucose Metabolism 14

Successful transition from insulin pump therapy to glyburide treatment in a 5-month-old male infant with a KJN11 mutation

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Introduction: Permanent neonatal diabetes mellitus (PNDM) is a rare form of diabetes requiring insulin therapy. Patients with PNDM due to activating mutations of KJN11 can respond to sulfonylurea therapy with improvement in metabolic control and quality of life.
Case study: A 5 month old male infant was diagnosed with neonatal diabetes at 3 months of age. He presented in diabetic ketoacidosis with a Hemoglobin A1C (HBA1C) of 9.0 %(4.3-6.1). After stabilization with insulin drip, he was transitioned to pump therapy. By 5 months of age, total daily dose (TDD) of insulin : 3.5 - 4.6 units (70-89% of TTD as basal insulin). Once genetic testing confirmed mutation in KCNJ11:E227K, he was admitted for transition from insulin therapy to therapy with oral glyburide, a sulfonylurea. Goal dosing for glyburide was 2.5 mg BID(1 mg/kg/day). The glyburide starting dose was 0.625 mg qd and basal rate was decreased by 25%. Over a 4 day period, the glyburide was increased by 25% daily and basal rate was decreased by 25% daily. Based on the blood sugar profiles final dosing regimen was 1.25 mg of glyburide QID. He was successfully weaned off of insulin therapy with stable glucose levels 94 to 132 mg/dL in the 24 hours prior to discharge. At 6 months of age his HBA1C was 6.4 %, at 8 months of age 5.6 %. He remains off of insulin therapy with current glyburide dose of 1.25 mg tid.
Conclusion: Glycemic control with glyburide seemed superior to insulin pump treatment. No severe hypoglycemia or gastrointestinal side effects due to glyburide were observed. Our patient's growth parameters have been normal so far and family reported improved quality of life. Since however sulfonylurea treatment in patients with PNDM is still a very new treatment modality, longterm data on continued efficacy/ side effects are needed.

P2-d3-944 Glucose Metabolism 14

Octreotide-induced long QT syndrome in a child with congenital hyperinsulinaemia

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Introduction: Congenital hyperinsulinism (CHI) is inappropriate insulin secretion from β-cells of pancreas due to various genetic causes. Here, we report a CHI case under octreotide treatment, which developed long QT, and therefore underwent subtotal pancreatectomy for definite cure of CHI.
Case: A thirty-five-day old male infant received the diagnosis of CHI on the 3rd day of his life in an epicenter and referred to our endocrinology clinic for further follow-up and management. Despite multiple drug treatment his hypoglycemia persisted therefore he underwent a near-total pancreatectomy at the 8th month of his life. The histopathological diagnosis was compatible with diffuse hyperinsulinism. Mutation analysis revealed that the patient was a compound heterozygote for a novel missense Mutation (p.Met115Val) inherited from his mother and a nonsense mutation (p.Trp1339X) inherited from his father in the *ABCC8* gene. On the other hand, during the follow-up, a long QT (0.49) was determined on the ECG examination, which was normalized after withdrawal of octreotide. Therefore, the long QT was considered to be secondary to Octreotide treatment.
Conclusion: ECG monitoring before and during octreotide treatment in order to recognize long QT and prevent related complications in cases with congenital hyperinsulinemia is critical.

P2-d3-945 Glucose Metabolism 14

A novel mutation for thiamine responsive megaloblastic anaemia and diabetes

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Background: Thiamine responsive megaloblastic anemia with diabetes and deafness (TRMA) syndrome is an early onset autosomal recessive disorder characterized by megaloblastic anemia, sensorineural deafness and diabetes mellitus, other reported findings are congenital cardiac malformations and optic atrophy, Thiamine found to correct anemia and to lesser degree diabetes but has no effect on deafness, Mutation in the SLC19A2 gene encoding thiamine transporter protein THTR-1 is found to be responsible for the disease, we report a novel mutation in the SLC19A2 & long term follow up in a female Saudi patient.
Objective and hypotheses: The aim of this study is to describe anew case of TRAM & diabetes and define the underlying gene defect.
Methods: DNA analysis was performed on the index case, here parents and siblings, sequence analysis of SLC19A2 gene then done.
Results: A child of first -cousin parents presented at age of 18 months with hyperglycemia and anemia, deafness noted 1 year later treatment with thiamine corrected the anemia and hyperglycemia , DNA sequencing showed homozygous for a novel mutation (c905 G >A) in the SLC19A2 gene.
Conclusions: A novel mutation c 905 G>A was detected in a new case of thiamine responsive megaloblastic anemia and diabetes (TRAM).

P2-d3-946 Glucose Metabolism 14

Hyperglycaemia and kidney disease: which MODY can be suspected?

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Introduction: Maturity-onset diabetes of the young (MODY) is a group of monogenic disorders characterized by mild hyperglicemia. Up to now 13 different gene mutations responsible for different phenotypes have been reported. Clinical characteristic may suggest appropriate genetic analysis.
Case: We report about a 16 years old Italian girl who was referred to our Centre for glycemic variability in patient with right kidney hypoplasia, bladder instability, mild fasting hyperglicemia (6.94 mmol/L, n.v. < 5.5). Laboratory data showed absence of β-cell autoantibodies and HbA1c normal level (4.82 %). Oral glucose tolerance test (OGTT) showed normal glucose tolerance, increased insulin response. Family history was positive for impaired glucose tolerance and diabetes mellitus in both parents pedigree. During follow up hypoglycemia followed by responsive hyperglycemia was reported. Due to these clinical features, (dysglycemia and kidney abnormalites) *HNF1β* molecular sequencing and GCH Array were performed. Negative result induces us to consider other MODY among the 13 forms described. Since kidney abnormalities have been described also in HNF1α/MODY3, we screened by direct sequencing *HNF1α* gene. We found a novel variant (c.226 G>A; p.Asp76Asn) both in patient and in her father, who was suffering from diabetes. This missense change has never been previously reported in literature, and its biological role is still unknown.
Conclusions: The evidence of a significant family history of hyperglycemia and glycemic variability should be investigated in order not to miss cases of MODY. We suggest to consider genetic testing for MODY3 in patients with glycemic variability and kidney abnormalities even in absence of clinical diabetes which in MODY3 patients usually develop later than other forms.

P2-d3-947 Glucose Metabolism 14

Changing profile of GAD and IA2 positivity in children with type 1 diabetes in India

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Background: There are published data to show that approximately 60 % of type 1 diabetes patients in India are antibody positive. Similar data was seen from our group up to 2008.
Objective and hypotheses: We wanted to see the number of newly diagnosed patients with type 1 diabetes who were antibody positive at the present time. We felt that widespread polio immunization may lead to an alteration of antibody positivity.
Methods: All newly diagnosed type 1 patients had GAD and IA-2 antibodies measured by a standard method between 2004 and 2012.
Results: A total of 124 patients under the age of 21 years were studied. Antibody positivity was defined as positivity of either GAD or IA-2 antibody. In the cohort seen between 2004 and 2008, positivity rate was 61%. In the cohort seen between 2008 and 2012, positivity rose to 85%.
Conclusions: The major public health change that took place in India at this time was universal usage of oral polio vaccine. It is possible that oral polio vaccination resulted in higher antibody positivity in the target population of persons under 21 years age.

P2-d3-948 Glucose Metabolism 14

Evaluation of depression and glicaemic control of teenagers with type 1 diabetes

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Background: Psychiatric status especially in chronic diseases may worsen the disease outcomes and treatment adaptation. Type 1 diabetes mellitus (T1DM) mostly affects young people who are more tendency to psychiatric diseases such as depression during follow up.
Objective and hypotheses: We aimed to investigate the depression rate and increased depression symptom level of teenagers with T1DM and evaluate the interaction of glycemic control of these patients.
Methods: The study composed of 295 T1DM outpatient teenagers whose ages range from 11 to 18 years taking at least 6 months insulin therapy and their parents. Children Depression Scale (CDS), State Trait Anxiety Inventory for Children, Family Oriented Perceived Social Support Scale were applied to evaluate the depression and anxiety level of patients and Beck Depression Scale, State Trait Anxiety Scale, Multidimensional Scale of Perceived Social Support applied for parents depression and anxiety level. The last documented hemoglobin A1c (HbA1c) levels of patients were noted in our outpatient clinics. We herein compared increased depressive symptoms of our patients with glycemic control index.
Results: Mean score of CDS was found 11,25± 6,15. Significant positive correlation was noted between increased depressive symptoms with HbA1c levels ($p< 0,01$) and age of the patients ($p< 0,001$), but there was not a significant correlation with duration of disease ($p< 0,05$).
Conclusions: Other than physical problems, psychiatric problems of these patients with T1DM should not be ignored in clinical grounds. Chronic process of the disease, intensive treatment regimen, younger age and follow-up procedures should take this risk into account in diabetic teenagers.

P2-d3-949 Glucose Metabolism 14

Neonatal hypoglycaemia due to glucose 6 phosphatase deficiency

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Introduction: Glycogen storage disease type I (GSDI) is a rare autosomal recessive disease with an estimated incidence of 1: 100,000 live births. It results from a defect in the glucose-6-phosphatase (G6Pase) required for the hydrolysis of glucose-6-phosphate into glucose. GSDI can be caused by defect in the catalytic subunit G6P-α (type Ia) expressed in liver, kidney and intestine, codified by *G6PC* gene; or by defects in the ubiquitously expressed G6P transporter (type Ib), codified by *SLC37A4* gene.
Patient: The patient was a 10-month-old girl who was born preterm with 2.7 Kg from consanguineous parents (first cousins). She had refractory hypoglycemia and generalized seizures since 3 months old. At the first evaluation, she had normal height (72 cm) and weight (8.9 kg) for age. She was unable to support her head. A moonface, ocular hypertelorism, small nose with anteverted nostrils, carp mouth with high palate, and hepatosplenomegaly were observed. At the laboratory evaluations, a high triglycerides (305 mg/dL), uric acid (11.4 mg/dl) and lactate (8.0 mmol/L) levels were observed.
The presence of fasting hypoglycemia with persistent hepatosplenomegaly suggested GSDIb. Genetic-molecular study identified a homozygous inactive mutation in *SLC37A4* gene.
Glucocorticoid was gradually withdrawn and gastrostomy was performed for enteral feeding at brief intervals. The patient died at the age of 2.8 year due to sepsis of intestinal origin.

Discussion: Blockage of the glycogenolysis and gluconeogenesis leads to hyperlactacidemia, hyperlipidemia and hyperuricemia. In GSDIb patients, dysfunctional neutrophils cause recurrent infections, mucosal ulcerations and inflammatory bowel diseases. Renal failure is a late complication due to progressive proteinuria. Treatment aims prevent hypoglycemia through continuous feeding.
Conclusion: Neonatal hypoglycemia associated to visceromegaly, recurrent infection and typical facial features can be a clue to the diagnosis of GSDIb.

P2-d1-950 Growth 3

The determinants of short stature in HIV infected children

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Background: Short stature in children can be caused by chronic illnesses like untreated HIV infection.
Objective and hypotheses: The aim of this study was to assess the association between short stature and HIV clinical variables-viral load,CD4 count,adherence,being on HAART vs not being on HAART.
Methods: Pertinent data was obtained by retrospective review of the electronic medical records (EMR) of all patients attending the Botswana-Baylor Children's Clinical Centre of Excellence (COE). Patients were grouped into various catergories: WHO immunological category (CD4 count or %), viral load, age(1-18 years),sex,level of adherence(%),height and whether receiving HAART. For each category the proportion of patients with height for age Z score (HAZ) score less than -2 SD and -3 SD was determined using WHO anthro/anthroplus software. Short stature was be defined as HAZ < -2 SD and profound short stature was defined as HAZ< -3SD. The Epimax table calculator was used to determine the statistical differences between the groups and p-value < 0.05 was considered statistically significant.
Results: The children with severe immunosuppression (CD4%< 15%) were 3.3 times more likely to have profound short stature compared to those with CD4%>15% (OR:3.30,CI:1.51-7.09, P=0.002), males were 1.5 times more like to be stunted compared to females (OR:1.49,CI:1.19-1.87, P=0.001). Those with treatment failure (VL>400) were 2.6 times more like to have profound short stature compared to those with suppressed viral load (VL< 400) (OR 2.64, CI 1.27-5.38, P=0.008) and those with poor adherence (Adherence< 95%) were 1.7 times more like to have profound short stature compared to those with good adherence (adherence>95%(0R 1.72, CI 1.03-2.05, p=0.037).
Conclusions: Poor adherence, severe immunosuppression and treatment failure were associated with profound short stature.These prelimary findings call for further studies into causal relations between these clinical variables and short stature.

P2-d1-951 Growth 3

Idiopathic short stature: final results of the growth evolution and analysis of the *GH1, GHR* and *IGF1* genes in a control study with therapeutic intervention

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Background: The term "Idiopathic Short Stature" (ISS) is used to describe short stature for which no underlying pathogenesis or aetiology is known. Among the factors that may cause growth retardation in these children, genetic alterations in the GH-IGF1-skeletal system have been proposed. Our interest in the study of ISS in the last decade has focused on the study of molecular alterations involved in its pathogenesis and on the search for effective therapeutic alternatives.
Objectives:
1) To determine the treatment option that achieves the best final height SDS in children with ISS.
2) To detect genetic alterations in *GH1*, *GHR* and *IGF1* in ISS patients.
Methods: Prospective clinical trial with randomaized assignment to three treatment groups: Group I, control; Group II, GnRHa and Group III, GH + GnRHa. The study was approved by the ethical committee. In all these patients auxological, biochemical and hormonal characteristics were evaluated. DNA was extracted from leukocytes by standard procedures. *GH1*, *GHR* and *IGF1* genes were directly sequenced after PCR amplification.
Results: We found that the combined treatment of GH+GnRHa was the best therapeutic option. The genetic study showed the P1 intron 4 (rs2665802) as the most frequent variation in *GH1*. The *GHR* gene showed the exon 3 deletion in 48 % of patients. In addition two heterozygous mutations were found in this gene. The most frequent variation in *IGF1* were c.-219-1191T>C and c.*297A>T, 30% of the patients not presented any alterations and one of them presented a novel mutation.
Conclusions: This study could provide important information for the basic knowledge about the therapeutic management and genetic basis of ISS.

P2-d1-952 Growth 3

Autosomal recessive (type I) is more frequent than autosomal dominant (type II) isolated growth hormone deficiency in a cohort of Brazilian patients

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Background: Isolated GH deficiency (IGHD) is a clinically and genetically heterogeneous disorder. Deletions, frameshift and nonsense mutations in *GH1* are responsible for severe autosomal recessive IGHD (type I) and are rare in European cohorts. The autosomal dominant (type II) is the most frequent genetic form of IGHD and is caused mainly by mutations that affect splicing of *GH1*. Patients with IGHD type II have substantial variation in the severity of GH deficiency.
Objective and hypotheses: To assess defects in *GH1* gene in children with short stature and different degrees of GH secretion status.
Methods: We selected 112 children evaluated at our center with postnatal short stature
(height SDS < -2), low IGF-1 levels and GH stimulation tests response peak less than
3.3 µg/L (n = 32), between 3.3 and 5 µg/L (n = 18) and from 5.1 to 10 µg/L (n = 62). Pituitary MRI was performed in all patients with GH peak < 3.3 µg/L and all of them had eutopic posterior lobe and an intact stalk (inclusion criteria). Exclusion criteria were known causes of short stature and other pituitary hormone deficiencies. Deletion of *GH1* gene was assessed by MLPA or restriction enzyme digestion only in patients with severe GH deficiency (GH peak < 3.3 µg/L). The entire coding region of *GH1* was sequenced in all patients.
Results: Mutations in *GH1* gene were only identified in patients with GH peak < 3.3 µg/L. Autosomal recessive IGHD due to *GH1* deletion was identified in 7 patients: 6 in homozygous state and one in compound heterozygosity with c.171+5G>C located in intron 2. One patient heterozygous for GH1 c.291+1G>T at the donor splice site of intron 3 had the autosomal dominant form.
Conclusions: In this cohort of Brazilian patients, defects in *GH1* gene were only identified in patients with severe IGHD. The autosomal recessive form of IGHD was more common (7/32, 22%) than the autosomal dominant form (1/32, 3%).

P2-d1-953 Growth 3

Breast milk analytes and infancy growth

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Background: Suggested benefits of human breast milk (HM) include reduced later obesity. Previous HM studies are small, and few address growth outcomes.
Objective and hypotheses: To investigate relationships between HM total calorie content (TCC), %macronutrients, and infancy growth. We hypothesise that specific HM composition may relate to slower weight gain in breast-fed infants.
Method: HM hindmilk samples were collected at 4-8 weeks postnatally, pooled over 2-4 weeks, in a large cohort, with detailed infancy anthropometry. Triglyceride (fat), lipid analytes (including omega-3 &-6 fatty acids) and lactose (carbohydrate) were measured using ^{1}H-NMR. Protein was measured by precipitation & freeze drying. TCC was calculated using Atwater conversions and %macronutrients(of TCC) determined.
Results: In 614 HM samples, fat (mean±SD) was:2.8±1.5g/100mls, carbohydrate (carb): 8.4±0.7g/100mls, protein:1.9±0.4g/100mls. TCC was 66.5±14.6kcal/100mls. HM of mothers exclusively breast-feeding vs. mixed feeding was more calorific (68.4±14.9 vs. 63.5±13.6kcal/100mls,p< 0.0005), with greater %fat, less %carb and less %protein. Subsequent analyses were adjusted for nutrition type, sex, gestational age and birthweight. TCC was inversely related to 12m adiposity(p=0.02). HM %fat was inversely related to adiposity gain, %carb positively related, and %protein unrelated (table 1). No associations were seen with length.

	%Fat	%Carbohydrate	%Protein
12m W	p=0.2	p=0.2	p=0.7
3-12m W	B-0.08,p=0.02	B0.008,p=0.02	p=1.0
12m SF	B-0.008,p=0.004	B0.01,p=0.001	p=0.8
3-12m SF adiposity gain	B-0.007,p=0.02	B0.01,p=0.01	p=0.9

[Table 1:adjusted]

Linoleic acid (LA) was the single lipid to show independent inverse correlation with 12m adiposity.
Conclusions: HM samples from a large cohort show greater TCC from mothers exclusively breast-feeding. Independently, %fat was inversely related, potentially mediated by LA, whilst %carb positively related to later infant adiposity.

P2-d1-954 Growth 3

Polymorphism rs8081612 in the mitogen-activated protein 3 Kinase 3 (*MAP3K3*) gene is associated with children height in a Brazilian cohort

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Background: Previous studies identified several SNPs associated with adult height. However, the influence of these SNPs on the height variation in children is uncertain.
Objective: To study the impact of five SNPs on the height of well-nourished and healthy children, attending private schools in the city of Fortaleza, Brazil.
Methodology: We selected 1008 students aged between 4 and 9 years. The selection of the genes and SNPs were based on previous GWAS of human height: CDK6 (rs2282978); SOCS2 (rs3782415); IGF1R (rs2871865), MAP3K3 (rs8081612) and MMP24 (rs2425019). DNA samples from oral mucosa were obtained and SNPs were genotyped by allele-specific PCR real-time. All genotypes are distributed in Hardy-Weinberg equilibrium. To test for an association for each SNP a simple linear regression analysis was performed, considering genotype as independent variable additive and height SDS as the dependent variable. Variables that had p< 0.05 in simple linear regression analysis were selected for multiple linear regression analysis, to assess the presence of independent effect of each of the polymorphisms. All statistical analysis was performed by SigmaStat for Windows (version 2.03, SPSS, Inc., San Rafael, CA).
Results: We confirmed the association of SNP rs8081612 in MAP3K3 gene and height variation in children (p = 0.044). We estimate that rs8081612 explains 0.4% of population variation in height with an increased height of 0.54 cm per T allele. This association was in the same direction and intensity of previous GWAS in adult height. No association was found with the other SNPs.
Conclusions: This is the first association study in Brazilian children looking for SNPs that could account for height variation. The association of rs8081612 in MAP3K3 gene and children height need to be confirmed in other population.

P2-d1-955 Growth 3

Identification of FGFR3 and SHOX mutations in patients with hypochondroplasia and Léri-Weill dyschondrosteosis: clinical overlap or clinical misdiagnosis?

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Introduction: Léri-Weill dyschondrosteosis (LWD) and hypochondroplasia (HCH) are characterized amongst other features by disproportionate short stature due to mesomelic and rhizomelic shortening of the limbs, respectively. It is known that mutations in *SHOX* or its enhancers, localized in the pseudoautosomal region 1 (PAR1), are found in ~70% of LWD, whilst mutations in *FGFR3* are identified in ~70% of HCH cases, the majority due to a common mutation, p.N540K.
Objective: To determine if there is a genetic overlap between LWD and HCH.
Methods: Genetic analysis of the coding exons of *FGFR3* (NM_000142.4) in 136 LWD individuals with no known PAR1 defect. Mutation screening of *FGFR3* and *SHOX* and its enhancers in 62 HCH patients, previously excluded for mutations in *FGFR3* ex12, including p.N540K. Mutation screening was undertaken by HRM, sequencing and MLPA (*SHOX*/PAR1). Pathogenicity of novel alterations was assessed by cosegregation analysis, estimation of their frequency in the normal population and bioinformatic tools.
Results:
1) No *SHOX* mutation was detected in the HCH patients and no *FGFR3* mutation was identified in the LWD cohort;
2) A total of 10 *FGFR3* variants were detected in 13 (21%) HCH patients: three known pathogenic mutations (p.S279C (2), p.K650T, p.R669G), three possibly pathogenic mutations (p.L377R, p.A352V, p.L608V) and four non-pathogenic changes (p.D139A, p.F195L, p.F384L (2), p.P449S (2)).
Conclusions:
1) No *SHOX* mutations were found in HCH patients.
2) No *FGFR3* mutations were identified in our PAR1 negative LWD cohort.
3) Our results do not support the existence of a genetic overlap between LWD and HCH. Differential clinical diagnosis of HCH and LWD is often difficult in infancy and childhood and is only evident when the characteristic growth patterns and/or X-ray features develop.
4) *FGFR3* missense variants were detected in a significant number of HCH patients but care must be taken to determine their pathogenicity.

P2-d1-956 Growth 3

Incidence of SHOX deficiency in a cohort of Italian children with idiopathic short stature

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Background: The short stature homeobox-containing (SHOX) gene, located in the telomeric pseudoautosomal region 1 (PAR1) on the short arm of both sex chromosomes, is important for linear growth. SHOX deficiency is not only the cause of Leri-Weill dyschondrosteosis but is also involved in idiopathic short stature (ISS).
Objective and hypotheses: The aim of this study was the assessment of SHOX deletions and mutations in children with ISS in order to estimate the frequency and clarify possible genotype/phenotype correlations.
Methods: This study, supported by the Eli Lilly Italia and approved by the Italian Society for Pediatric Endocrinology and Diabetes (ISPED), is a multicenter study including several Italian Pediatric Endocrinology Units. We collected almost 100 blood samples from patients with ISS and various degree of skeletal alterations. Genomic DNA was extracted and used for Multiplex Ligation-dependent Probe Amplification (MLPA) and sequencing analysis. MLPA was performed using the SALSA MLPA P018-F1 SHOX probe mix kit analyzing both the coding region and the enhancer of the SHOX gene in the Pediatric Laboratory of Parma.
Results: Out of the first 50 patients analyzed, 5 presented a big deletion of the SHOX gene, including the sister and mother of one of the probands. Other 3 patients showed an alteration of cytokine receptor-like factor 2 (CRLF2) and arylsulfatase F (ARSF) genes, being these genes involved in cell proliferation and bone/cartilage composition, respectively. Three patients had a complex genetic asset of chromosome X to be confirmed. No mutations were detected by sequencing.
Conclusions: In our cohort of patients with ISS the incidence of SHOX gene deletions is 6%, in accordance with some of the previous reports. Auxological measurements of body proportions (mesomelia), the presence of minor skeletal abnormalities, and the search for subtle radiographic signs are important keys leading to the appropriate indication for genetic analysis.

P2-d1-957 Growth 3

Final adult height and body proportions in young adults with childhood onset (CO) and adult onset (AO) Crohn disease (CD)

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Background: Short stature is a known complication of Crohn's disease (CD) in childhood but less is known on the impact of childhood onset disease on adult height and body proportions.
Objective and hypotheses: To assess final adult height and body proportions in 49 adults [27.4 (6.4) yr; F: 30; M: 19] with childhood (CO) or adult (AO) onset CD.
Methods: Body weight, height (Ht) and sitting height (SHt) were measured and converted to SD scores. Parental heights were self-reported by the participants and mid-parental height (MPH) was calculated.
Results: In women there was no significant difference in height, sitting height or BMI z-score between participants with CO and AO (Table 1). In contrast men with CO had a significantly lower HtSDS, BMI and SHt SDS than those with AO and were also much lower than their respective MPH (Table1). There was no correlation between BMI, Ht, SHt SDS with age at diagnosis, age at recruitment or disease duration for the CO group. BMI positively correlated with age at diagnosis in the whole group (r=0.46, p=0.03).

	Female				Male			
	CO		AO		CO		AO	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age Diagnosis(y)	13.7	2.4	25.5+	5.2	11.8	2.15	23+	3.3
Age Recruitment(y)	23.4	4.4	31.8+	5.7	22.3	4.6	30.7+	4.1
Height SDS	-0.1	1.1	-0.1	0.8	-1.0*#	0.9	0.4+	0.6
Delta MPH SDS	0.0	0.8	-0.1	0.7	0.6	0.7	-0.4+	0.8
Sitting height SDS	-0.6	1.1	-0.6*	0.6	-1.2*	0.7	0.2+#	0.5
BMI SDS	0.1	1.8	0.8*	0.9	-0.3	1.4	1.2*+	1.3

[Table 1]

* $p< 0.05$ compared with UK 1990; + $p< 0.05$ CO vs AO same gender; # $p< 0.05$ between genders of same type of CD; Delta MPH: Target - Actual height SDS.
Conclusions: Short stature and skeletal disproportion in childhood onset of CD track into adulthood. Obesity is more common in AO CD which may reflect a higher usage of oral steroids in this group.

P2-d1-958 Growth 3

Electronic auto-injection device prevents growth hormone wastage in comparison to non-electronic injection devices

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Background: Mean adherence in patients treated with recombinant human growth hormone (r-hGH) using the easypod™ has recently been demonstrated. Overall adherence was high with 91.2 % injections administered as prescribed. However there were significant differences in adherence between prepubertal (96,5 %) and pubertal (89,2 %) patients.
Objective and hypotheses: To evaluate adherence over the first four years of r-hGH treatment under everyday conditions as well as amount of r-hGH prescribed respectively administered with the easypod™ in comparison to non-electronic devices (n-e-d).
Methods: Retrospective, observational, open-label, non-controlled, single centre study in patients diagnosed growth hormone deficient (GHD), small for gestational age (SGA) or Turner Syndrome (TS). Patients were treated with

r-hGH either using the easypod™ or n-e-d. For patients using n-e-d adherence was determined by the ratio of prescribed to returned vials. Easypod™ is the only automated electronic injection device for rh-GH (Saizen®) delivery that accurately records dose and injection time to evaluate adherence.
Results: Data from 46 easypod™ patients, mean 11,1 ± 3,2 years, and 91 n-e-d device using patients mean age of 10,5 ± 3,3 years, treated with r-hGH were analyzed.
In the first r-hGH treatment year patients using n-e-d showed a mean adherence of 93,1 %, mean adherence of easypod™ patients was 88,0 %. In the second year of r-hGH treatment adherence dropped to 83.1 % in patients using n-e-d whereas in patients using the easypod™ adherence was slightly higher than in the first year of treatment (89,5 %). 23 % of patients using n-e-d had a severe wastage of r-hGH up to 25 %. In contrast patients using easypod™ device had no wastage of r-hGH.
Conclusions: Easypod™ is the only device able to objectively measure r-hGH treatment adherence with an overall good adherence over the first four years of treatment and moreover saves drug in comparison to non-electronic injection devices.

P2-d1-959 Growth 3

Growth pattern in Kabuki syndrome

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Background: Kabuki syndrome is a multiple congenital syndrome with diverse clinical features including developmental delay, facial dysmorphology, hypotonia and short stature. In 2010 a mutation in the MLL2 gen was discovered in two thirds of the Kabuki syndrome patients.
Objective and hypotheses: In Kabuki syndrome, almost all patients have postnatal growth retardation off which the cause is still unknown; investigation of the growth patterns was opportune.
Methods: Data for this growth study in individuals with Kabuki syndrome were collected from referring clinicians from the Netherlands, Belgium and Austria. Subjects were eligible for inclusion in the study if the following criteria were met: a genetically confirmed (MLL2 mutation) diagnosis of Kabuki syndrome and no current treatment with growth hormone or other drug that could influence growth. 56 subjects met the inclusion criteria for this study and were sent a consent form and questionnaire.
Results: We present a limited report on growth data (n=37) with a genetically confirmed diagnosis of Kabuki syndrome. The growth data from the research population were compared with Dutch reference values. The data showed that postnatal growth retardation is a clinical feature in all cases. Postnatal height SDS ranged from -2,5 to 3,3 (mean 0,18) and the current height SDS ranged from -6,24 to -0,09 (mean -2,8) in all individuals. 26 (=70,3%) patients had a height SDS below -2 SD and so fulfilled the definition of short stature.
Conclusions: Since all Kabuki syndrome patients have a growth deflection during childhood and a diminution or absence of the pubertal growth spurt, a defect in the growth hormone/IGF-I axis is very likely. Further research is warranted to clarify the cause of this postnatal growth restriction. We hypothesize an altered body composition similar to that in children with Prader-Willi syndrome. Therefore, we will start a study including growth hormone therapy in children with Kabuki syndrome.

P2-d1-960 Growth 3

Heterozygous expression of a new acide-labile subunit (ALS) mutation: anthropometric and biochemical characterisation and response to growth hormone therapy

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Introduction: Acid-labile subunit (ALS) deficiency due to homozygous inactivation of the ALS gene is associated with short stature, very low circulating levels of ALS, IGF-I and IGF-binding protein-3 (IGFBP-3) and a poor response to growth hormone (GH).
The impact of ALS mutations heterozygosity on growth is unknown.
Case study: We describe a ten years-old girl with severe short stature (height: -3.2 SDS) heterozygous for a new ALS mutation, her clinical and biochemical characteristics and the response to GH treatment.
The girl showed short stature and low circulating IGF-I (-2.8 SDS), IGFBP-3 (-3 SDS) and ALS(-1.9 SDS) levels and normal GH secretion.
We found a novel heterozygous frameshift ALS mutation resulting in a premature stop codon (c.1283delA, p.Gln428Arg fsX440) co-segregating with short stature in the patient family. Size-exclusion chromatography showed a reduction by about 55% of the IGF-I, IGFBP-3, and ALS 150 kDa ternary complex compared with a normal control.
IGF-1 generation test performed with three different GH dosages showed a good response in term of increase in IGF-1 level and a dose dependent increase in formation of ternary complex at size-exclusion chromatography.
Clinical response after 6 months of therapy with GH was satisfactory (height velocity increased form 3 cm/year to 8 cm/year).
Conclusions: We describe a case of severe short stature due to a heterozygous ALS mutation and document a good biochemical and clinical response to GH. We suggest that 1) ALS mutations in heterozygous state can be responsible for a subset of patients with severe short stature (below -2.5 SDS), low IGF-1 (below -2 SDS), normal GH secretion; 2) the identification by genetic assessment of this subset of patients could help in the administration of the appropriate therapy.

P2-d1-961 Growth 3

Adherence to the treatment with ZOMAJET™, a needle-free device transjecting growth hormone: results of French observational survey

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Background: Treatment of growth hormone (GH) deficiency using needle injections may be not well tolerated, because of pain and needle phobia, leading to non-compliance. The use of needle-free devices is believed to improve patient adherence to treatment.
Objective: To evaluate the global treatment compliance rate with the Zomajet needle-free device (Zomajet Vision X or Zomajet 2 Vision) over a 3-year period.
Population and methods: This was a multicentre, longitudinal, observational survey in patients with documented GH deficiency. Patients were followed at regular intervals for a maximum 3-year period according to the usual practice. Compliance was evaluated according to parent/caretaker questioning. Reasons for non-compliance and/or for stopping the treatment were noted. The global compliance was defined as the ratio between the cumulative treatment duration self-reported by the parent/caretaker and the total treatment duration prescribed by the investigator at the previous visit. Missing treatment durations were matched to zero (maximum bias method).
Results: 83 patients with an age of 9.5 ± 3.8 (mean ± SD)) with GH deficiency (mean height standard deviation score -2.2±1.0 SD) were enrolled by 18 paediatric endocrinologists. Most patients were naïve from GH therapy and were treated with Zomajet for a mean duration of 1,8 yrs. Over the 3-year follow-up, the global compliance rate was 96.6 ± 9.1% (95%CI [94.6-98.6%]).

A high compliance rate (> 90%) was obtained both in children and in adolescents. Annual size gain was 8.8 ± 2.2 cm the first year, 7.7 ± 1.8 cm the second year and 5.8 ± 1.8 cm the third year. Local intolerance due to the device was reported in 16.9% episodes at least at one transjection.
Conclusions: The Zomajet needle-free device provides a high compliance rate over 3 years confirmed by relevant annual clinical outcomes and a good tolerance.

P2-d2-962 Growth 4

Clinical features of a series of patients with Rubinstein-Taybi syndrome from Brazil

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Background: Rubinstein-Taybi syndrome (RTS) is a rare genetic disease characterized by multiple congenital anomalies including short stature.
Objective and hypotheses: To report the clinical features of a series of patients with RTS from Brazil.
Population and/or methods: Sample consisted of patients diagnosed in two hospitals from southern Brazil during the last 10 years. We performed the collection of the clinical data from their medical records.
Results: The final sample was composed of 7 patients, 5 male and 2 female, ages at first evaluation ranging from 5 days to 5 years and 10 months. Four patients consisted of two pairs of monozygotic twins. Six patients (85.7%) presented growth delay, five of them of prenatal onset (the length at birth ranged from 42 to 45 cm). The main clinical features observed consisted of palpebral fissures slant downward (100%), broad thumbs with radial angulation (100%), high arched palate (85.7%), broad great toes (85.7%), micrognathia (71.4%), microcephaly (57.1%) and capillary hemangioma (57.1%). Four of the 5 males (80%) had cryptorchidism. Unusual findings, each observed in 1 patient, included postaxial polydactyly, accessory nipple, club feet, Dandy-Walker malformation and partial dysgenesis of corpus callosum. All patients evolved with neuropsychomotor delay. One patient (14.3%) presented a congenital heart defect, a ventricular septal defect with necessity of surgical treatment. Dysphagia and constipation were verified in two patients each (14.3%). Four patients underwent karyotypic analysis, with normal results.
Conclusions: Despite RTS be considered a syndrome of postnatal growth retardation, the majority of our patients presented a growth delay of prenatal onset. It is also noteworthy in our sample the frequency of monozygotic twins observed. Among the more than 600 cases of RTS reported in the literature, at least 12 sets consisted of monozygotic twins. Maybe, the twinning may be related to the etiology of this condition.

P2-d2-963 Growth 4

Microcephalic osteodysplastic primordial dwarfism type II with severe insulin resistance

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Background: Microcephalic osteodysplastic primordial dwarfism (MOPD) is a group of disorders similar to Seckel syndrome. Three subtypes (type I-III) have been reported.
Objective and hypotheses: We report on a 14.5 year of girl who presented with intrauterine growth retardation, severe postnatal failure to thrive, facial dysmorphism and skeletal dysplasia. The clinical and radiologic findings were consistent with MOPD II. In adition to previously published features she also showed clinical and laboratory findings of severe insulin resistance. Our patient was the first child of the consanguineus Turkish parents. Her birth weight at term was 1.6 kg. Neuromotor development was mildly retarded. At the examination, her height was 102.5 cm (Ht SDS: -9.5), weight 30 kg (Wt SDS: -3.6), head circumference 46 cm(HC SDS:-7), sitting height/height ratio 0.57, BMI was 28.2 (BMISDS :2.8). Her bone age was 15 years (Greulich-Pyle). She was at Tanner stage 5. She had a high forehead, prominent nose, retrognathia and small teeth. Characteristic skeletal abnormalities were lumbar hyperlordosis, bilateral coxa vara, flaring of the distal femoral metaphysis, cranial displacement of the patellae, brachymetacarpia and clinodactyly-V. She also had generalized obesity, acanthosis nigricans with mild hirsutism. This clinical findings were consistant with insulin resistance. Thyroid function tests revealed mild hypothyroidism. Adrenal function, IGF-1 and growth hormone stimulation tests were normal. Glucose 191 mg/dl and insulin above 400 mu/L at 120 min on oral glucose tolerance test. Karyotype analysis was 46 XX and cranial MRwas normal.
Results: Direct sequencing of the coding region and the flanking intronic sequence of the exon 30 of the pericentrin(PCNT) gene in the DNA sample of the patient revealed the homozygous splice site mutations IVS30-2A>G.
Conclusions: Few patients are reported with this type of dwarfism. More case reports are needed to better delineate this rare type of MOPD.

P2-d2-964 Growth 4

Comparison of serial bone age determination by BoneXpert image analysis and manual assessment using Greulich and Pyle method in children with congenital adrenal hyperplasia

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Background: Skeletal maturation, or bone age (BA), is typically assessed by comparing a radiograph (X-ray) of the left hand and wrist with standards for normal children using the atlas method of Greulich & Pyle (GP). The assessment done manually by radiologists or pediatric endocrinologists (PE) requires expertise with the methodology and remains subjective and variable.
Objective: To determine the sensitivity of BoneXpert (BX) image analysis software based on the GP method to identify advanced BA and rapidly changing BA in serial BAs in children with Congenital Adrenal Hyperplasia (CAH).
Methods: A PE and a radiologist, blinded to patient data other than gender, determined BA using GP method in children with CAH (n=35, 11 male; mean age 9.7±0.3 yr; range 1.3-16.8; mean 3.8 BAs at 0.7±0.0 yr intervals). The sensitivity of BX measurements to identify advanced BA (>1 yr above chronologic age (CA)) and rapid changes in BA was determined.
Results: BAs in this cohort of children with CAH were advanced 1.6±0.2 years by manual estimation and 1.1±0.2 years by BX. 69 BAs were advanced >1 yr compared to CA as assessed by both manual observers. BoneXpert correctly identified 52 of the advanced BAs (Sensitivity =75%). On serial evaluation by both manual observers, 8 BAs were advancing >50% faster than CA over the interval between BAs. BoneXpert correctly identified 6 of the rapidly advancing BAs (Sensitivity =75%).
Conclusion: The BX method estimates BA a mean of 0.5 years younger than manual estimation. This may be a systematic difference between the methodologies. BX calculates values across the spectrum rather than assigning the BA of the closest standard. However, underestimation of BA may limit the utility of this methodology in conditions with advanced BA such as CAH or precocious puberty. Prospective studies are needed to assess the utility of the BX methodology for guiding clinical decisions in children with conditions associated with advanced BA.

P2-d2-965 Growth 4

Growth retardation and autoimmune hypothyroidism with skeletal dysplasia based on mutation in ACP5 gene (Spondylenchondrodysplasia)

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Background: Spondylenchondrodysplasie (SPENCD) is a syndrome featuring short stature with skeletal dysplasia, diverse neurological signs, and variable autoimmune features. The first patient with a typical SPENCD was clinically described in 1976, the molecular basis was unravelled 2011 by one of the co-authors.
Objective and hypotheses: Here, we describe a variable clinical expression of compound-heterozygous mutations in the *ACP5* gene, coding for tartrate-resistant phosphatase (TRAP).
Method: We present a 12 year-old girl presenting with profound growth retardation (height -3.4 SDS) and autoimmune hypothyroidism as manifestation of SPENCD, together with her mother and brother bearing the same mutations.
Results: Radiologic evaluation showed typical features of SPENCD. CNS-imaging revealed massive enlargement of the adenohypophysis as a consequence of hypothyroidism and characteristic cerebral calcifications without neurological abnormality. Thyroxine treatment lead to significant catch-up growth. Adenohypophysis normalized within 6 months. Besides autoimmune thyroiditis, she reported episodes of Raynaud's phenomenon. Otherwise, no findings indicated significant autoimmune disease. Family testing revealed the same genotype also in two siblings, who showed appropriate height within the genetic target range and only minor skeletal abnormalities (discrete platyspondyly without enchondromatosis). Although peripheral T-cells were slightly decreased in the mother, extensive immunological and endocrinological analysis revealed no signs of autoimmunity in both family members carrying two mutations in *ACP5*.
Conclusions: In summary, this family extends the clinical spectrum of *ACP5* mutations towards minor variants with only subtle skeletal abnormalities and normal final height in two affected family members. Investigating the molecular basis for the clinical variability in SPENCD may contribute to the understanding of the complex pathophysiology of autoimmune diseases.

P2-d2-966 Growth 4

Short stature by SHOX gene deletion due to a chromosomal traslocation

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Background: A translocation involves an exchange between two pieces of two chromosomes. Can be balanced or unbalanced. The latter results in loss or gain of genetic material. The SHOX gene is located in the pseudoautosomal region of the short arms of chromosomes X and Y. The clinical phenotype is characterized by short stature and limb shortening mesomelic.
Methods: We report two cases of SHOX gene deletion by chromosome translocation using Microarray CHG.
Results:
Case 1: Girl, 14 forwarded by stature 144.4 cm (-2.43 SD). Normal body proportions, Tanner V. Height Mother: 152.1 cm. Height father: 172cm. Target height: 156 + / - 5 cm (-1.2 SD). Karyotype: adding material on the short arm of chromosome X (formula chromosomal: 46, X add (X) (p 22)). Normal parental karyotype. Microarray CHG (180K): the extra material from a translocation with a Y chromosome microdeletion Xp22.3 exist Yp11.2 duplication of 2,418 Mb and Yq11.221-q12 of 43.294 Mb.
Case 2: Child 8 months sent by rhizomelic shortening of limbs. Height 67.4 cm (-2.06 SD). Normal body proportions, except breaststroke decreased (64 cm). Height father: 180 cm, height mother 157.1 cm. Target height: 175.05 ± 5 cm (-0.36 SD). Map Bone shortening of humerus and femur. Karyotype: 46, X, der (Y) (q10, q10) translocation between the long arms robertsioniana Y chromosome. Normal parental karyotype. Microarray CHG (60kb) Yp11.32 deletion, duplication Yq11.21-q11.23 duplication of 14.087 Mb and Yq12 of 0.234Mb.
Conclusions:
1. The importance of early and accurate diagnosis of SHOX gene alterations set an appropriate treatment strategy in patients with short stature.
2. When a chromosome translocation is important to exclude the gain or loss of genetic material.

P2-d2-967 Growth 4

Familial isolated growth hormone deficiency due to P89L mutation

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Introduction: The autosomal dominant form of isolated growth hormone deficiency type II (IGHDII) is mostly caused by splicing mutations in intron 3 of the GH1 gene. However, different missense mutations within the GH1 gene also cause familial autosomal dominant IGHDII by interference with the GH1 cellular secretory pathway.
Case study: We are presenting two patients - a girl and her mother - with IGHDII carrying a rare autosomal dominant mutation. The girl was born at term; birth weight and length were 2450 g (-2.4 SDS) and 45 cm (-1.6 SDS), respectively. She presented with short stature (-3 SDS) at the age of 4.5 years. X-ray of the wrist showed delayed maturation (-3 SDS). GH peak values were 2.3 ng/ml (L-dopa test) and 1.8 ng/ml (clonidine test). The IGFI value was 45 ng/ml. The thyroid hormone and cortisol levels were within the normal range and MRI showed a normal pituitary gland. She is being treated with rhGH for 3 years now, and after the initial catch-up growth, she is following the 50th percentile. Her mother, at the age of 38, was also very short (133 cm) but was never diagnosed or treated. No other pituitary hormone deficiency was detected and the MRI was also normal. DNA sequencing of the GH1 and GHRHR genes in the child revealed the dominant heterozygous P89L mutation in exon 4 of the GH1 gene (c.344C>T), which was also identified in the mother.
Conclusion: The P89L mutation has been demonstrated to cause profound growth hormone deficiency associated with multiple pituitary hormone (TSH and ACTH) deficiencies. Although the latter may appear after the diagnosis of growth hormone deficiency, their absence in our two patients shows that the P89L mutation might also cause IGHDII. The reason for the variability in the clinical presentation of P89L carriers remains to be elucidated.

P2-d2-968 Growth 4

Study on the defect of SHOX gene and its conserved noncoding elements (CNE) and the relationships with phenotypes and X-ray in idiopathic short stature (ISS)

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Background: The human SHOX gene is one of the major genes contributing to longitudinal growth. Heterozygote mutations or deletions of the SHOX gene and its CNE have been reported in some individuals with idiopathic short stature . Therefore, our research concluded the indicators of skeleton changes in X-Ray and phenotypes in idiopathic short stature**.** which can use to picking out the patients with SHOX gene deficiency from ISS.
Objective: Study on the defect of SHOX gene and its conserved noncoding elements (CNE) and the relationships with phenotypes and x-ray in patients of idiopathic short stature(ISS).
Methods: Using sequencing and micro satellites analyses the variations in CNE and the upstream and downstream of SHOX gene in 501 cases; then, investigated the relationships with phenotypes and x-ray of patients with ISS

of normal gene and normal controls.
Results:
1) The group of CNE abnormity together accounted for 36 cases (7.19%), and male had 20 cases, female had 16 cases; the group of SHOX gene abnormity together accounted for 22 cases(4.39%), and male had 12 cases, female had 10 cases; In the female, the CNE abnormalities may be more effected on forearm; the SHOX gene abnormalities impact leg development apparently.
2) The clinical manifestation was similar between CNE abnormalities compared and the SHOX gene abnormalities in male;
3) The X-ray bone characteristic indexes reflecting the ulnaris of radial epiphysis fused in advanced, for all the prepuberty patients, only included angle of distal ulna and radius diminished; for all the puberty patients, In female had height between the distal ulna and radius increased, angle of inclination of ulna and included angle of distal ulna and radius diminished, in male only included angle of distal ulna and radius diminished.
Conclusion: The defect of SHOX gene and its conserved noncoding elements (CNE) had the relationships with phenotypes and x-ray in patients of idiopathic short stature(ISS).

P2-d2-969 Growth 4

Identification of an intragenic SHOX duplication and FGFR3 mutation (p.K650T) in a family with multiple members affected by disproportionate short stature

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Introduction: Hypochondroplasia (HCH) and Léri-Weill dyschondrosteosis (LWD) are autosomal dominant skeletal dysplasias. Clinical features of HCH are similar to achondroplasia, but tend to be milder and some are often subtle or absent. Short stature and the characteristic Madelung deformity (MD), the bowing of the radius and distal dislocation of the ulna, are features of LWD. Mutations in *FGFR3* and *SHOX* are found in ~70% of HCH and LWD, respectively.
Case study: Boy born at term, BL 49cm (-0.84 SDS) and BW 3410g (0.09 SDS). In early childhood, he was suspected to have HCH but the common *FGFR3* mutation, p.N540K, was not identified. Radiological examination detected mild MD at age 10.5 years, which was then also observed in the mother, suggesting LWD. The mother had disproportionate short stature (138cm, -4.03 SDS) whilst the father was of normal height (169cm, -0.86 SDS). The proband's sister was born at term (BL 43cm, -4.02 SDS; BW 2500g, -2.21 SDS). Although, at 15.2 years, she had disproportionate short stature (140.7cm, -3.35 SDS), clinical and radiological examination revealed the absence of MD. *Molecular analyses: SHOX* and *FGFR3* were screened by HRM, sequencing and MLPA. PAR1 haplotype analysis was undertaken using a panel of microsatellite markers. An intragenic *SHOX* duplication (exons 2-6a) was detected in the proband and mother but absent in the sister. Haplotype analysis revealed that no common PAR1 allele was shared between the two siblings, suggesting the implication of an additional locus in the affected sister. Mutation analysis of *FGFR3* revealed a pathogenic heterozygous mutation (c.1949A>C, p.K650T) in all three family members.
Conclusions: The phenotype observed in both the proband and his mother is caused by two different mutations: an intragenic *SHOX* duplication and the *FGFR3* p.K650T mutation. The sister inherited only the *FGFR3* mutation, which explains why she presents with disproportionate short stature but no MD.

P2-d2-970 Growth 4

The heart and aorta MRI usefulness in the diagnostics of girls with Turner syndrome

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Background: Congenital heart defects are found in high percantage of girls with Turner syndrome (TS). The majority of these defects are present in the left heart. The evaluation of cardiovascular system is therefore an important element in the diagnostic work-up of TS and is of particular significance in safety aspects of recombinant growth hormone treatment (rGH).
Objective and hypotheses: The aim of the study was to assess the cardiovascular system in girls with TS with magnetic resonance imaging of the heart and aorta (CMR).
Methods: 19 girls with TS, aged 15.7 yrs, were analyzed. Echocardiography was performer in all, CMR in 17/19 and angioMR in 13/19. 17 patients was treated with rGH in a mean dose 0,045 mg/kg/d for a mean period of 4,5 yrs. CMR was performed using 1,5 T Magnetom Avanto machine (Siemens). AngioMRI was performed with a gadoline contrast agent and type TWIST sequence. The assessment of aorta was analyzed on nine levels. With a volumetric method using a CINE sequence the morphology and function of left and right ventricle were obtained. "Phase contrast" type sequences served for the assessment of a flow through the aorta and pulmonary truncus.
Results: All patients had normal morphology and function of left and right ventricle. There were no differences between CMR and echocardiography. The following abnormalities were found in angioMRI: recoarctation of the aorta with a dilating ascending aorta in 1 (1/13; 7.7%), right-sided course of descending aorta in 1 (1/13; 7.7%), persistent left superior vena cava junction with a coronary sinus (1/13; 7.7%) and thus giving 23.1% (3/13) in total.
Conclusions: CMR, particularly angioMRI, allows to detect vascular abnormalities of the aorta and their prospective evaluation should be monitored for a safe rGH treatment in girls with TS.

P2-d2-971 Growth 4

Hyperbolic function shows close correlation between GH secretion (GH) rate and GH sensitivity

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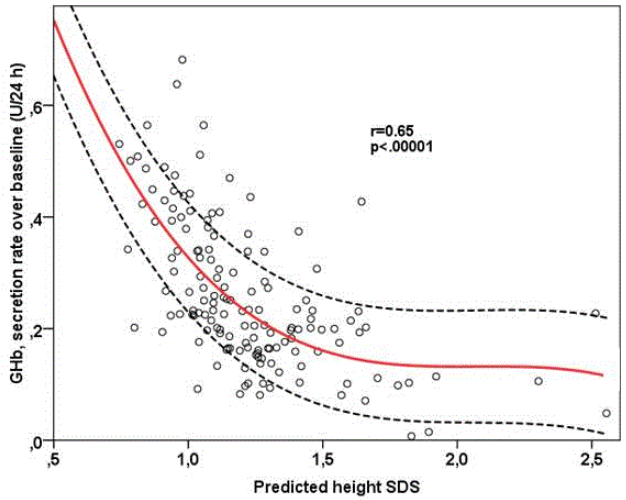
Background: Impressive similarities exist between the insulin resistance-associated metabolic syndrome and untreated GH deficiency in both children and adults. Central findings are visceral obesity and cardiovascular morbidity. At present it is debated if children with lower GH sensitivity but GH secretion within age and gender related references like in idiopathic short stature (ISS) belong to a continuous spectrum of imbalanced GH secretion in relation to sensitivity or not.
Objective and hypotheses: The relationship between GH secretion and GH sensitivity is following the one known for insulin. 128 short prepubertal children with a broad range of secretion and sensitivity were included.
Methods: From the 24-hour GH profile (72 x 20 min), the 24h GH secretion rate was estimated with a deconvolution method. The secretion rates above the basal level (PULSAR) (GHb) and above zero (GHt) were used. GH sensitivity was estimated from the predicted growth response to GH treatment using a prediction model.
Results: A hyperbolic function was found between GH sensitivity (predicted height SDS) and GHb ($r=.65$, $p< .00001$) and GHt ($r=.60$, $p< .00001$).



[GH secretion rate in relation to GH sensitivity]

Conclusions: As well-known from the relationship of insulin secretion and sensitivity described by a hyperbolic function, a similar hyperbolic function was found capable to describe the relationship between GH secretion rate and GH sensitivity. Our data confirms functional similarities between insulin and GH in addition to its closely related post-receptor pathways.

P2-d2-972 Growth 4

Plasma midkine concentrations in healthy children and children with short stature

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Background: Midkine (MDK) is a paracrine growth factor that, in mice, is highly expressed in early life in multiple organs, including the growth plate. The role of midkine in human growth is unknown.
Objective: To examine associations of plasma MDK with age, sex, adiposity, and short stature in children.
Methods: Plasma MDK was measured by immunoassay in two cohorts of healthy children. To assess associations with age, we studied a South Korean cohort (n=71) of diverse age (0 - 18 y) but comparatively uniform BMI. To assess associations with adiposity, we studied an older U.S. cohort (n=73; mean age, 15.8 y; range 5 to 24.3 y) with diverse BMI standard deviation score (SDS; range, - 0.67 to + 3.2). MDK was also measured in a group of U.S. children with short stature (mean height SDS, -2.05), including idiopathic short stature (ISS) (n=22), constitutional delay (n=3), growth hormone (GH) deficiency (n=1), and small for gestational age (n=4).
Results: In healthy children, MDK concentrations declined with age (R^2=0.41, p< 0.001), with values highest in infants (0.75 ± 0.12 ng/mL, mean ± SEM), lower at ages 1-4 y (0.32 ± 0.02 ng/mL) and lowest in older children, ages 5-18 y (0.24 ± 0.01 ng/mL). Plasma MDK did not differ significantly between males and females and did not correlate with BMI SDS or percent total body fat. In 29 of 30 subjects with short stature, MDK concentrations did not differ significantly from normal subjects, regardless of diagnosis or GH treatment status, and did not correlate with height SDS or IGF-1 SDS. One subject with severe ISS receiving GH treatment had extremely high plasma MDK (13.8 and 15.6 ng/mL on two occasions).
Conclusions: In healthy children, MDK concentrations are highest in infants and then decline with age and are not significantly influenced by sex or adiposity. To establish whether abnormalities involving MDK cause human growth disorders requires further investigation.

P2-d2-973 Growth 4

Adult height in individuals with Silver-Russell syndrome treated with growth hormone from childhood - correlations to pubertal growth

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Background: Silver-Russell syndrome (SRS) is characterized by intra- and extrauterine growth retardation. Growth hormone (GH) treatment has a positive outcome if started several years before puberty.
Objective: To determine the effect of GH treatment in SRS on pre- and pubertal growth, as well as on adult height (AH).
Methods: 20 prepubertal children (12 males) with SRS followed at a national centre at Queen Silvia Children's Hospital, were treated with GH from a mean (SDS) age of 3.7 (1.1) years (age range between 2.0-7.0) until achieved AH (age ranged between 13-18 years). All were born SGA with a birth weight of 1800 (617) gram and birth length of 41 (5.5) cm. Ten children were born preterm (six due to maternal preeclampsia). Midparental height ranged from -1.85 to 1.6 SDS with mean maternal height -0.4 (0.9) SDS and paternal height -0.3 (1.0) SDS. GH dose ranged between 0.03-0.05 mg/kg/day. GnRH analogue treatment was given due to early puberty in 4 girls and 4 boys. GH treatment was stopped when velocity was < 1 cm/yr and AH was measured at 18 years of age.
Results: Mean height SDS at start of treatment was -3.8 (1.4) and within two years a rapid catch-up was seen of 1.6 (1.4) SDS, giving a height SDS of -2.2 (1.4), *P*< 0.01. Height at start of puberty was -1.2 (1.4) SDS, *P*< 0.01 and the total prepubertal height gain was 2.6 (1.4) SDS. During the puberty, an earlier deceleration of growth was seen compared to the normal population. When AH was reached, 6 males had heights above -1 SDS (mean -0.7 (0.5)), and the group of the other 6 males had a mean height of -1.9 (0.6) SDS and the female group -3.2 (1.6) SDS. Bone age development could not predict the early fusion of bone plate.
Conclusion: Treatment with GH leads to a substantial height gain during prepubertal years, whereas pubertal years lead to a premature termination of growth spurt. Further investigation of the effect of sex steroid levels during pubertal years on bone maturation in SRS patients is needed.

P2-d3-974 Growth 5

Comparative analyses of prevalence of thinness, overweight and obesity of semi-urban Nigerian school children using three international references

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Background: Growth is a sensitive index of a child's health, undernutrition still being a problem in developing countries, while obesity is a public health epidemic worldwide.
Objectives and hypotheses: Prevalence of thinness, overweight and obesity among girls and boys in a semi-urban Nigerian community is dependent on reference and definition used.
Methods: Cross-sectional study of body mass index (BMI) and socioeconomic status (SES) of 1611 primary school (8 public, 8 private) children: 800 boys, 811 girls aged 5-11 years using a multi-stage stratified random-sampling technique, 2009-2010. References used were:
1) the US CDC birth cohort 1929-1974 ($CDC_{29<}$),
2) the Swedish birth cohort 1974 (SW_{74}), both with BMI_{SDS} cut-off < -1.5 for thinness, +1.5 for overweight, >+2 for obesity, and 3) the Cole's definitions of thinness grades -1, -2 and -3, of overweight +1 and of obesity +2. SES was assessed by a 5graded scale (I -V) for both parents.
Results: Thinness: There were no significant age trends or gender differences. SW_{74} indicated higher prevalence of thinness, 18.5%, than did the CDC_{29} reference, 15.7%, p< 0.001. By Cole grades 1, 2, 3 of thinness, 29%, 7%

and 3% were identified. The prevalence of thinness increased ($p< 0.01$) with SES, 9.1%, 6.1% for SES I versus 22.3% and 20.8% for SES V, for SW_{74} and $CDC_{29<}$, respectively.
Overweight/Obesity: There was a significant negative trend for overweight/obesity with age, ($p< 0.001$) with the highest prevalence of 4.3% at 5 years and 0% if 9 & 10 years old. SW_{74} identified 20/9 overweight/obese children, and $CDC_{29<}$ 13/2 overweight/obese children. Prevalence of overweight and obesity were 1.3%, and 0.1% using Cole's reference. More overweight/obesity was found in private schools and in higher SES families.
Conclusions: In Nigeria, thinness remains prevalent in lower SES whereas overweight/obesity increase in lower age groups in families with higher SES.

P2-d3-975 Growth 5

Pituitary gland size is a useful marker in diagnosing growth hormone deficiency in short children

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Background: Diagnosis of growth hormone deficiency (GHD) in children necessitates a battery of tests which are not always reliable. Confirmatory diagnostic criteria are necessary prior to commencing a long-term treatment of GH replacement. Pituitary hypoplasia can be seen in children with isolated GHD, however, confirmatory studies of this correlation are lacking and usefulness of this marker in particular age group and puberty status is debated. The study aims to test the possible application of pituitary gland (PG) size on MRI as a marker of GHD at different age and puberty status.
Methods: Children diagnosed with GHD fulfilling clinical, biochemical and radiological criteria were enrolled. Brain MRI scans were done. Height (Ht) and width (Wd) of PG were measured by a single observer (GR). Size of PG was calculated as $(Ht \times Wd)^{3/2}$. A control group of age and sex-matched children was recruited. Categorical data were compared between the two groups using two-tailed Chi-squared test and analyzed using SPSS.
Results: 52 patients (36 males) were enrolled and were compared to 130 (65 males) controls. The median and age range were 11 years (3-16) and 9 (2-17) for patients and controls respectively. PG size was compared between the 2 groups. Median PG size was 216 mm (42-650) vs 371 (56-1128) ($P = 0.002$) for patients and controls respectively. A subgroup of patients over the age of 10 (Tanner stage II-III) was studied. It consisted of 30 patients and 57 controls. Median PG size for patients and controls was 289 mm (144.0-786.43) and 468 mm (55.96-1381.19) respectively ($p < 0.001$).
Conclusions: Pituitary size, obtained by a simple formula from a 2 D MRI image, can be a useful marker in the diagnosis of GHD particularly in pubertal children. This marker can be used to compliment the diagnosis of GHD in selected patients when the results of GH stimulation tests are non-confirmatory. Obtaining a population-specific normative data for comparison enhances the marker validity.

P2-d3-976 Growth 5

Growth and pubertal timing in patients with phenylketonuria (PKU)

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Background: PKU is a disorder of aminoacid (AA) metabolism due to phenylalanine hydroxylase deficiency to convert phenylalanine into tyrosine. In order to prevent mental retardation, a diet restricted in natural protein and supplement with phenylalanine-free AA mixtures is required. While the positive results of dietary treatment on neurological outcome are already known, long term effect on growth and puberty have not been enough documented.
Objective and hypotheses: To study growth, puberty, Body mass index (BMI) and Final height /Target height (FH/TH) in PKU pts.
Methods: 48 treated pts with PKU (21 females-F, 27 males-M) diagnosed by newborn screening from 1979. All subjects born at term with normal weight. Chronological age (CA) was < 3 yrs (0.24-2.64) in 13/48 pts and >3 yrs in 35/48 pts. Growth measurements were taken at 3, 6 yrs and pubertal onset (B2, T4) using Italian growth charts. FH/TH was evaluated.
Results: Evaluation at 3 yrs was performed in 26/35 subjects (14 F,12 M): mean F's height was 95.15 (84-105) cm, BMI 15.8 (11-17.2); mean M's height was 96.27 (88-107) cm, BMI 16.8 (15-19.1). Evaluation at 6 yrs was performed in 25/35 pts (12 F, 13 M): mean F's height was 120.18 (101-144) cm, BMI 17.3 (13.7-21.4); mean M's height was 116 (103.3-126.5) cm , BMI 16.9 (15.4-21.6).
24/35 pts (10 F, 14 M) were evaluated at pubertal onset (breast and testicular stage according to Tanner): mean age of B2 was 10.7 (7.6-11.4), mean F's height was 138.5 (130.3-152) cm, BMI 19.5 (15.7-23.7), mean CA at menarche was 12.7 (11.64-14.16); mean age of T4 was 11.11 (6.8-15.4), mean M's height was 141,8 (131.9-153.5) cm , BMI 19.4 (15-22).
22/24 pts reached FH (10 F, 12 M): F FH/TH 0.99(0.95-1.02); M FH/TH 0.99(1.01-0.99).
Conclusions: Although a poor natural protein intake growth, BMI,CA and H at pubertal onset were normal. Menarche occurred at similar time of female population. FH were according to TH in all subjects.

P2-d3-977 Growth 5

Endocrine complications in patients with β-thalassemia Major

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Background: β-thalassemia major is an inherited hemoglobin disorder characterized by chronic anemia and iron overload due to transfusion therapy and gastrointestinal absorption. Iron overload causes severe endocrine complications in patients with multi-transfused β-thalassemia major . Endocrine complications includes short stature , acquired hypothyroidism and hypoparathyroidism, hypogonadism, glucose intolerance and diabetes mellitus.
Objective: The main objective of this study is to determine the prevalence of prominent β-thalassemia major complications.
Methods: Eighty-seven patients entered the study in our hospital. The patients have a mean age of 10.5 (range, 5-16) years . Physicians collected demographic and anthropometric data and the history of therapies as well as menstrual histories. Patients have been examined to determine their pubertal status. Serum levels of ferritin, glucose, insulin, A1c, cortisol, ACTH,calcium, phosphate, PTH were measured. Thyroid function was assessed by T3, T4 and TSH. IGF-1 in serum was determined.
Results: Short stature was seen in 32.2% (28/87)of our patients. Diabetes mellitus was present in 10.3%(9/87), Primary hypothyroidism and hypoparathyroidism was present in 6.9%(6/87) and 1.15%(1/87) of the patients. Hypocalcemia was 9.2%(8/87) . Cortisol, and ACTH were normal.About 10.3 %(9/87)of patients had more than one endocrine complication with mean serum ferritin of 3125 micrograms/lit.IGF-I standard deviation score (SDS) was low, that is, below -2SDS, in 47.1%(41/87) of patients.
Conclusions: A high frequency at endocrine dysfunctions seen in β-thalassemia major patients included: short stature, diabetes, primary hypothyroidism and hypoparathyroidism and hypocalcemia. High prevalence of endocrine complications among our thalassemics signifies the importance of more detailed studies along with therapeutic interventions.

P2-d3-978 Growth 5

IGF-1 levels in term SGA children with catch up at 12-18 months

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Background: Rapid weight gain early in postnatal life is associated with adult metabolic diseases. This linkage is due to alterations in programming of insulin, IGF-I and IGF-II during catch up growth (CUG). But literature in Indian population is limited.
Objective and hypotheses: To estimate IGF-1 levels in term SGA (< 10thpercentile) babies at 12-18 months and its association with CUG in our cohort.
Methods: Fifty term SGA children 12-18 months were enrolled. Birth weight and length recorded from discharge document and current weight and length

measured at inclusion. Data analyzed for CUG as gain in weight or length SDS or both >0.67 (percentile band). IGF-1 levels measured in post-glucose load (1.75gm/kg) sample using ELISA kit.
Results: Average birth weight, length, gestational age was 2.1± 0.3 Kg, 44.4 ± 3.1 cm, 38.3± 1.3 weeks respectively. At enrollment mean age, weight and length was 15.0 ±2.1 months, 7.7 ± 1.3 Kg, 72.9 ± 5.6 cm. 60% (30) SGA infants showed CUG, 36% (18) and 50% (25) displayed CUG in weight (WCUG) and length (LCUG). IGF-1 level was 37.4 ± 54.4 ng/ml, significantly higher in CUG (56.6±63.2) vs NCUG (8.7±8.3) p=0.0, more in WCUG (66.1±73.4) than LCUG (37.8±52.8). IGF-1 positively correlated with weight/length SDS change from birth (r= 0.533, p=0.0), supporting its role in rapid postnatal CUG. Girls in LCUG (60%) were more than in NLCUG (32%), p=0.04, due to earlier linear growth in females.
Conclusions: More than 50% of infants born SGA showed CUG by 18 months and these children had significantly higher IGF-I levels.

P2-d3-979 Growth 5

Congenital hypopituitarism: clinical, biochemical and neuroradiological correlation

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Background: Congenital Hypopituitarism (CHP) exhibits an incidence of 1/53000 newborns. Clinical presentation is variable in severity and time. Early diagnosis can prevent damage to cognitive function or other resulting from associated deficiencies.
Objective and hypotheses: To evaluate clinical signs and symptoms present at early life stages and to analyze their relationship with hormone laboratory tests and diagnostic imaging in children with CHP.
Methods: Twenty nine patients were evaluated retrospectively: 16 females, 13 males, between 5 days and 10 years of age.
Results: Although a high proportion of the patients had history of neonatal hypoglycemia (52%), seizures (27%), micropenis (67%) and cholestasis (21%), only 3 patients (10%) were referred for suspected CHP during the neonatal period.The insufficient trophic pituitary hormones were GH 93%, TSH 76%, and ACTH 48%.Brain MRI of patients with multiple hormone deficiencies showed that 56% them had hypoplastic adenohypophysis, absence of stalk and ectopic neurohypophysis versus 28% of patients with isolated somatotrophic deficiencies.Three patients showed dysgenesis of the corpus callosum and two of them exhibited optic nerve hypoplasia.
Conclusions: Short stature in childhood is a relatively frequent reason for referral to a pediatric endocrine clinic, however, the information obtained from the medical history in the early months of life, which can provide valuable data for early diagnosis, is often neglected.
Although the presence of structural hypothalamic-hypophyseal abnormalities preferably leads to diagnosis of multiple pituitary deficiency, a proportion of those abnormalities are present in children with IGHD. This fact leads to the study of candidate genes and to the possible future expression of other associated deficiencies.

P2-d3-980 Growth 5

Phenotypic and genotypic variability in SHOX gene haploinsufficiency

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Background: SHOX gene haploinsufficiency is a relatively frequent genetic cause of short stature.
Objectives: To describe clinical features and molecular deletions-mutations of SHOX gene in a cohort of patients with SHOX gene haploinsufficiency.
Methods: SHOX/PAR1 molecular testing were performed by MPLA and sequencing.
Results: Pt1 presented short stature and some clinical features of Turner syndrome (TS like). Pt2 was diagnosed with Leri-Weill dyschondrosteosis (disproportionate short stature, mesomelia and Madelung deformity, LWD). 3 patients (pt3,4,6) presented short stature with mild anthropometric disharmony and dysmorphic features (SS). The others 4 patients presented idiophatic short stature (short stature with no specific findings other than growth failure, ISS). Pt1 had a complete SHOX deletion. The deletion found in Pt2 was similar to the deletion present in pt3, but the phenotype was very different. Others patients had a mutation in SHOX gene sequence.

Pt	S	Age	SH/H	AS/H	H, SDS	SHOX gene analysis	Phe
1	F	8	0,56	0,97	-2,1	Complete SHOX Deletion	TS like
2	F	13,8	0,58	0,96	-2,8	77 kb downstream PAR1 deletion	LWD
3	F	9,5	0,56	0,97	-1,4	20 kb downstream PAR1 deletion	SS
4	F	4,9	0,53	0,97	-2,7	c.414 G>C EX-3	SS
5	F	10,5	ND	1,01	-1,9	c.545-10 T>C INTR-4	ISS
6	F	5,6	ND	0,95	-2,3	c.55 C>T INTR-1	SS
7	F	15,5	ND	1	-1,7	c.397 C>G EX-3	ISS
8	M	6	0,54	1,01	-2,5	c.100 A>T EX-2	ISS
9	M	12,5	ND	0,99	-1,2	c.100 A>T EX-2	ISS

[Phenotype and genotype]

Abbreviations: S (sex), SH/H (sitting height/height), AS/H (armspan/height), Phe (phenotype), ND (no data available).
Conclusions: SHOX gene haploinsufficiency causes a wide spectrum of short stature phenotypes including patients with TS, LWD, short stature with mild anthropometric disharmony and dysmorphic features and only short stature (ISS). It is not possible to find correlation between genotype and clinical expression.

P2-d3-981 Growth 5

Comparative analyses of prevalence of short and tall stature of semi-urban Nigerian school children using three international references

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Background: Growth is a sensitive index of a child's physical and mental health. Short stature is the result of poor linear growth. Growth references of healthy children aid detection of extremes such as short and tall stature, however influenced by the secular trend.
Objectives and hypotheses: Prevalence of short/tall stature in girls and boys in a semi-urban Nigerian community is dependent on calendar year of reference population.
Methods: Cross-sectional study of height and socioeconomic status (SES) of 1611 primary school
(8 public, 8 private) children, 800 boys, 811 girls aged 5-11 years using a multi-stage stratified random- sampling technique 2009-2010. Short/tall stature were defined as $height_{SDS}$ outside ±2, 1) using US CDC birth cohort 1929-74 ($CDC_{29<}$), 2) Swedish birth cohorts 1956 (SW_{56}) and 3) 1974 (SW_{74}). SES was assessed using a 5graded scale (I -V).
Results:
Short stature: The prevalence of short boys/girls increased significantly with age. In all combinations of gender, age groups, and overall the SW_{74} reference gave a significantly ($p< 0.05$) higher prevalence 28% vs. 20% for SW_{56} and 15% for $CDC_{29<}$. The prevalence of short stature was higher ($p< 0.001$) in public 34%, 25%, 19% than in private schools 17%, 11% and 8%, for SW_{74}, SW_{56}, and CDC_{29} respectively. Moreover, increasing prevalence of short stature with decreasing SES
($p< 0.00001$) was found: 69%, 53% and 41% at lowest IV/V SES, vs. 26%, 14%, 8% at highest I/II SES, for SW_{74}, SW_{56} and $CDC_{29<}$.
Tall stature: Overall, the prevalence of tall stature was small and the SW_{56} yielded highest, 1%
(n=15 children), followed by CDC_{29}, 0.9%, (n=14), and SW_{74}, 0.6%, (n=10). No significant difference of the prevalence was found with age and between genders.
Conclusions: Prevalence of short/tall stature is highly dependent on the calendar year of birth of the references used, nevertheless, height is socioeconomic dependent.

P2-d3-982 Growth 5

Clinical, biochemical and neuroimaging findings as predictors of growth hormone deficiency (GHD) in children

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Background: Growth hormone stimulation testing (GHST) has been used as standard investigation in patients with clinical criteria suggestive of GHD. However, these tests are invasive and may raise safety issues, especially in a child with co-morbidities. Different studies aimed to identify risk factors for GHD but most focused on the differential diagnosis between idiopathic short stature and GHD in apparently healthy children.
Objective and hypotheses: To assess the association between GHD and the history of surgery or radiation of the sellar or suprasellar region or another anterior pituitary deficiency associated with specific clinical and imaging features, by evaluating the response to GHST.
Methods: Case-control study with retrospective clinical chart review of all patients meeting the criteria for GHST. GHD was diagnosed with GH peaks below 6 ng/ml (ECLIA) during sequential Arginine-Clonidine tests.
Results: 205 patients were analysed. 14/50 GHD patients had the postulated risk factors, while these were found in only 1/155 patients without GHD. There was a strong association between GHD and the existence of at least one of the postulated risk factors (Fisher's exact test $p< 0.0001$): the probability of having a risk factor was almost 60-fold higher (OR: 59.9, 95% CI 7.6-470.6) in the GHD group, and the risk of having GHD was approximately 5-fold higher (RR: 4.93, 95% CI: 3.56-6.81) in patients with one of the postulated risk factors.
Conclusions: Our findings clearly identified surgery of the sellar or suprasellar region, cranial radiotherapy and coexistence of congenital multiple pituitary hormone deficiencies with hypogenitalism in males, neonatal hypoglycaemia or cholestasis, diabetes insipidus or midline defects as major risk factors for GHD in paediatric patients meeting the criteria for GHST.

P2-d3-983 Growth 5

Longitudinal studies of growth and pubertal progress in adolescents with inflammatory bowel disease

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Background: Puberty and growth may be affected in inflammatory bowel disease (IBD) but the extent of these effects in adolescents is unclear.
Objective: To determine the impact of IBD on pubertal status and pubertal growth.
Methods: Prospective study in 45 adolescents (boys,23) with crohns disease (CD) and 18 (boys,12) with ulcerative colitis (UC) with a median age of 13.4yrs (range,10,16.6). Assessment included details of disease and anthropometry at 0 and 12 months and biochemical markers of growth and puberty at 0 months.
Results: The median HtDiag SDS, Ht0 SDS and Ht12 SDS for the overall groups were similar to the normal population, however, on sub-group analysis, the boys with CD were significantly shorter at 12 months ($p=0.048$). Individually, 10/45 (22%) adolescents with CD cases had one or more parameters of growth affected: 7 had HtDiagSDS < -2 and 6 had Ht0SDS and Ht12SDS < -2. None of the adolescents remained prepubertal beyond the age at which 97% of population would be expected to enter genital stage 2.
Median IGF1 and IGFBP3 SDS for the overall group was -0.43 (-5.81,2.62) and 0.43 (-1.93,2.66) respectively and were significantly different from the normal population ($p=0.03$ and $p< 0.0001$). IGF1 SDS and IGFBP3 SDS showed a significant association with Ht0 SDS in the whole group (r,0.365; $p=0.005$ and r,-0.318; $p=0.015$). ESR was found to be associated with HV and change in HtSDS in the whole group (r,-0.29;$p=0.03$ and r,-0.32;$p=0.02$) and with the IGF1:IGFBP3 ratio(r,-0.327$p=0.02$).
Median urinary LH:FSH, salivary testosterone (boys), and plasma INSL3 (boys) were not significantly different from sex and puberty matched healthy controls.
Conclusions: Disorders of pubertal growth are more likely to occur in CD. Achieving disease control may be important in attaining normal growth during puberty.

P2-d3-984 Growth 5

Measurement of birth length and parental height for SGA babies and follow-up of short children at 2 years

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Background: Small for Gestational Age (SGA) and Short Stature can be defined as birth weight (BW) and birth length (BL) ≤-2 standard deviations (SD). Affected neonates are classified as: (1) SGA, (2) Short, (3) SGA+Short. Most of these infants (60-70%) are healthy, constitutionally small individuals but others have been affected by intra-uterine growth retardation (IUGR). Without data on BL and parental height (PH), it is difficult to identify infants affected by IUGR who could benefit from later growth hormone (GH) therapy.
Objective and hypotheses: To determine the feasibility of: a) measuring BL and PH in infants with BW≤9th centile (UK 1990 reference data); b) re-measuring Short and SGA+Short children at 2 years (2y).
Methods: Trained Hearing Screening Assistants measured BL and PH for infants with BW≤9th centile between July 2008 - June 2009 within a single maternity unit. Infants were stratified based on BW and/or BL ≤-2SDS. Short and SGA+Short babies were re-measured at 2y.
Results: BW was recorded in 3797/3798 liveborn infants and was ≤9th centile in 481 (12.7%). BL was successfully measured in 341/481 (71%) of whom 47 were SGA (not Short), 46 Short (not SGA) and 60 SGA+Short. Both PH were measured in 52/153 (34%) infants. Of 107 eligible infants, 57 (53%) attended at 2y follow-up. Failure of catch-up growth was identified in 6/57 (11%) children of whom only 1 was already under medical supervision.
Conclusions: Measuring BL and OFC in children whose BW is SGA is feasible; 2y follow-up in short infants is useful in identifying the ~10% who have not caught up, and has now become standard practice in our unit. A second study is planned, aiming to increase the yield of BL and PH measurements in infants with BW≤9th centile so that height status at 2y can be interpreted in the context of the family pattern.

P2-d3-985 Growth 5

The effect of alteration in breast milk leptin concentration during a suckling period on neonatal weight gain

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Background: Leptin is involved in energy regulation. Breast milk leptin has been associated with neonatal weight gain.
Objective and hypotheses: To investigate whether the change in breast milk leptin content during a suckling period acts on neonatal body weight gain.
Methods: Total 37 lactating women and their infants were involved in the study. Breast milk were obtained from the same women before and after a suckling period in both the 10th and 30th days of lactation. Body weights of infants were measured before and after breast milk samples.
Results: Post-suckling body weight in both visit was increased, while breast milk leptin was not different. Pre and post-suckling body weight in the 30th

day of lactation was higher than that of the 10th day. Post-suckling breast milk leptin in the 30th day of lactation was higher than that of the 10th day, while pre-suckling breast milk leptin was not different. There was no correlation between the change in breast milk leptin and body weight gain in a suckling period. Changes in all parameters during lactation were expressed as delta. Delta pre and delta post suckling body weight were negatively correlated with both pre and post suckling breast milk leptin in the 10th and the 30th days of lactation.

Visits	Pre suckling body weight (g); mean±SD	Post suckling body weight (g); mean±SD	p
The 10th day of lactation	3267±433	3308±439	0.000
The 30th day of lactation	4046±588	4086±592	0.000
p	0.000	0.000	
Visits	Pre suckling breast milk leptin (ng/ml); mean±SD	Post suckling breast milk leptin (ng/ml); mean±SD	p
The 10th day of lactation	0.77±0.31	0.73±0.31	NS*
The 30th day of lactation	0.76±0.27	0.84±0.38	NS
p	NS	0.038	
*NS	Non significant		

[Table 1.]

Conclusions: The results of the study have suggested that the change in breast milk leptin in a suckling period is not associated with neonatal weight gain and that the change in milk leptin level during lactation might play a role in the regulation of weight gain in healthy neonates.

P2-d1-986 Growth 6

Concentration of selected metals in blood, plasma and urine of short stature and healthy children

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Background: The short stature in children is defined as height that is below the third percentile from the mean for age and sex.It is important to know the disorders in trace element status in humans, Both the alterations in the content and their mutual interactions may play role in the pathogenesis of short stature.
Objective and hypotheses: (1) to compare the content of Cd, Co, Cu, Fe, Mn, Zn, and Ni in blood, serum and urine of short stature and control group; (2) to estimate correlation between content of metals in various body fluids; (3) to investigate the correlation between the content of the elements and height, weight, age, place of residence; (4) to investigate the relationship between the concentration of selected metals and the use of hormone therapy.
Methods: The study was conducted on a group of 56 short stature children and 35 healthy childen. Metals were determined using High Performance Ion Chromatography and Inductively Coupled Plasma Mass Spectrometry methods.
Results: Our studies in children with short stature have shown a statistically significant increase content of Cd in the blood, Co in the serum and Cd and Cu in urine and significant decrease in the content of Zn, Co, Mn, Cu and Fe in the blood, Zn, Mn in serum and Zn, Fe and Co in the urine.
It was also noted statistically significant decrease in the content of Zn, Co, Mn, Cu and Fe in the blood, Zn, Mn in serum and Zn, Fe and Co in the urine. There were significant differences of Fe, Cu and Ni concentration among the groups with respect to the hormonal therapy. There were no significant differences between the groups with respect to type of area where respondents live. We observed no statistically significant differences between metal concentration and age, body weight and height.
Conclusions: Our study demonstrated statistically significant differences between the content of selected metals in body fluids of short stature and healthy children. Further research is needed in this area.

P2-d1-987 Growth 6

Genetic diagnosis of a patient with manifestations of both Prader-Willi syndrome and Angelman syndrome

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Introduction: Most cases of Prader-Willi syndrome are caused by partial deletion of the paternally derived chromosome 15, while maternally derived chromosome 15 is responsible for Angelman syndrome. We performed molecular and cytogenetic analyses to clarify the genetic background and make a definitive diagnosis of a patient with clinical manifestations of both syndromes.
Case study: The patient was a 15-year-old boy with type 2 diabetes. After birth, Prader-Willi syndrome was diagnosed based on fluorescence in situ hybridization (FISH), performed because of muscular hypotonia, failure to thrive, and bilateral cryptorchidism. However, at the age of 2 years, the diagnosis was revised to Angelman syndrome because of atypical absence, characteristic electroencephalographic discharges, mental retardation, and excessive laughter. He could not speak any meaningful words, or walk. He had hyperphagia, hypopigmentation, almond-shaped eyes, small hands and feet, and a large mouth and jaw. Chromosomal examination by G-banding stain revealed that the karyotype was a mosaic composed of 45,XY,der(1)t(1;15)(p36.3;q13),-15 and 46,XY,der(1)t(1;15)(p36.3;q13),-15 ,+mar. FISH did not detect signals of *SNRPN* with the probe for Prader-Willi syndrome or *UBE3A* for Angelman syndrome on the der(1) chromosome. Microarray based comparative genomic hybridization (array-CGH) also detected a 11.6Mb deletion in the region of chromosome 15q11.2q14, including the *SNRPN* and *UBE3A* genes. Methylation-specific PCR amplified the *SNRPN* gene using primers specific for the methylated gene.
Conclusion: We concluded that his diagnosis was Prader-Willi syndrome caused by the partial deletion of the long arm of chromosome 15, which had translocated onto chromosome 1. The clinical manifestations may have been modified by complex structural changes in the chromosomes. Since we suspect the additional complication of Angelman syndrome, we are now investigating possible mutations in the *UBE3A* gene.

P2-d1-988 Growth 6

Preterm twins with discordant birth weight: auxological, hormonal and metabolic follow-up during the first two years of life

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Background: Intrauterine growth retardation (IUGR) has been associated with an increased risk of health problems later in life. It has been argued if twins, with growth lower than singletons, could represent a natural model of IUGR. Few are the studies on the monitoring of discordant birth weight twins and on the possible health outcomes comparable to those of singletons born IUGR.
Objective and hypotheses: To obtain twin-to-twin pair data and to detect early indices of adult diseases, in a matched-pair prospective cohort study, auxological, metabolic and hormonal data have been investigated in twins with discordant birth weight >15%.
Methods: Twenty-four preterm twins (32-36 w of GA) have been quarterly followed for their first two years of life trough auxological (weight and length), metabolic (glycaemia, total and HDL cholesterol, triglycerides, ApoA1 and ApoB) and hormonal (insulin, IGF-1, cortisol, TSH and fT4) evaluations.
Results:
Growth pattern. Catch-up growth occurred in 80% and 100% of infants within the first and second year, respectively. In each pair of twins, a progressive trend to recover the discordance in weight and length has been observed.
Hormonal profile. Higher levels of TSH (in euthyroidism) [p=0.02] and cortisol (at 6 months) [p=0.033] have been found in IUGR with respect to AGA

infants. Higher levels of IGF-1 [p=0.03] and cortisol [p=0.0015] have been associated with catch-up growth of length and weight, respectively.
Lipid profile and insulin resistance. By considering the main metabolic indices (TG/HDL, ApoB/A1, I/G and HOMA-IR) IUGR didn't significantly differ from AGA subjects.
Conclusions: Our results in a series of 24 birth weight discordant twins don't seem to indicate severe auxo-metabolic-hormonal alterations during the first 24 months of life, notwithstanding cortisol and TSH significant increase in IUGR subjects. A longer follow-up in a larger population is necessary to confirm these preliminary data.

P2-d1-989 Growth 6

Sitting height/standing height ratio from birth to adulthood: normal reference values

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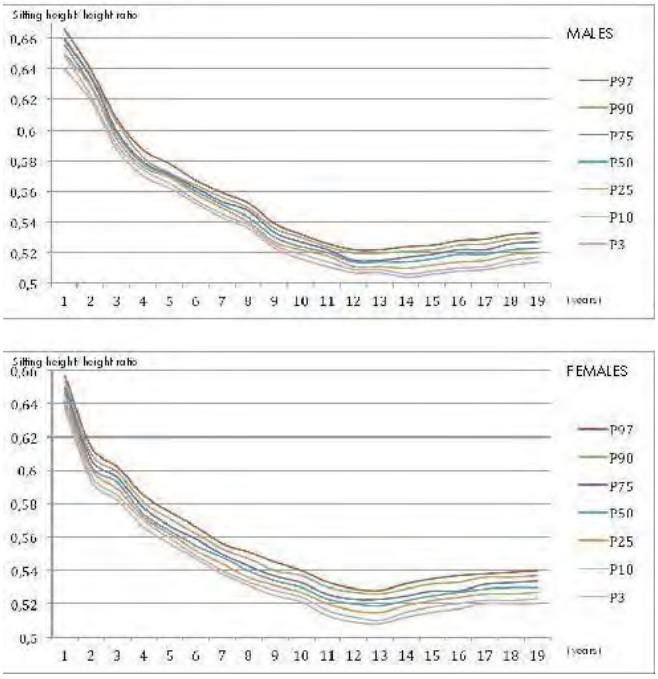
Background: The approach of children with growth retardation requires the assessment of body proportions.
Objective and hypotheses: To determine the normal values of sitting height (STH) / standing height (SH) ratio from birth to adulthood in a population from Aragón (Spain).
Methods: Longitudinal study from birth to 18 years; length (up to 3 years) and STH / SH (from 2 years) ratios were measured in 165 males and 167 females.
Results: The value of STH / SH ratio decreases in boys and girls from birth (0.656 and 0.647, respectively) until the onset of puberty (0.514 and 0.519, respectively), approximately at 11 years in females and 12 years in males. Afterwards it increases slightly, until it reaches the final adult STH / SH ratio (0.52 and 0.53, respectively).
Conclusions: Normal reference values of the STH / SH ratio from birth to adulthood are presented. This ratio decreases from birth to puberty and then increases slightly until final height is reached.



[Figure1. Sitting height/standing height ratio: percentile normal longitudinal values from birth to adulthood]

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Natural history of congenital growth hormone deficiency (GHD)

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Background: Among children with congenital GHD, about 40% remain deficient in adulthood. Further, GH treatment in adulthood remains controversial.
Aim: To analyze persistence of congenital GHD into adulthood in a Swiss patient cohort.
Methods: Retrospective analysis from 1998-2011 of 63 children with congenital GHD, all treated with GH (mean 9.5±3.6 yrs). At final height, children were re-tested (arginine stimulation or insulin tolerance test) for GHD following 4-month treatment cessation. Complete GHD was defined as a peak GH< 5 µg/L and partial as 5≤GH< 10 µg/L after stimulation. GH treatment was continued in adulthood when GH< 3 µg/L.
Results: At diagnosis, 16 (25%) had complete GHD while 47 (75%) exhibited partial GHD. At final height, persistence of complete GHD occurred in 9/16 (56%) children with complete GHD: 8/16 (50%) had a peak GH< 3 µg/L; 4/16 (25%) exhibited only partial GHD; 3/16 (19%) recovered with a peak GH>10 µg/L.
Among the 47 children with partial GHD at diagnosis, at repeat testing 3/47 (6%) had complete GHD (3< GH< 5 µg/L); 9/47 (19%) exhibited partial; 28/47 (60%) recovered and 7/47 (15%) were lost to follow-up. No children pursued GH treatment.
Conclusions: At repeat testing, complete GHD (defined by GH< 5 µg/L) was identified in 12/63 (19%) young adults with congenital GHD, 3 of whom had partial GHD at diagnosis. Notably, nearly half (31/63; 49%) recovered including 19% diagnosed with complete GHD and 60% with partial GHD. No child with partial GHD required GH treatment in adulthood (peak GH< 3 µg/L post arginine stimulation). These data suggest that these children may not need to be re-tested at the end of growth. More standardized stimulation tests, as insulin tolerance test, would help to confirm this recommendation. Genetic studies will be useful to characterize the molecular basis for recovery in children with congenital GHD.

P2-d1-991 Growth 6

Comparison of the WHO child growth standards and references and the Sempé and Pedron growth references in a population of 1023 Algerian children referred for short stature

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Background: Because of the absence of national references, the most widely used growth charts in Algeria are the French ones (Sempe and Pedron, 1979). The WHO standards and charts are rarely used in daily practice.
Objective: The aim of our study was to compare the WHO standards (≤5 years) and references (>5 years) and the Sempé and Pedron (SP) Growth references in the assessment of growth on a population of Algerian children referred for short stature.
Methods: Height (length) was measured in 1023 children referred for short stature. For each child, age- and sex- adjusted z-scores for height were calculated using both the WHO and the French growth data.
The children were divided into two groups (group1 ≤ 5 years old, group 2 > 5 years old).
Results:
In group 1 (356 children, 52% boys, mean age: 2.95± 1.4 years):
The mean Height z-score was significantly different for the two references

(SP: -2.46±1.62, WHO: -2.97±1.55; p< 0.001).
The percentage of children whose height for age z-score was < -2 SDS was higher using the WHO standards (69.9%) compared to the French references (59.5%), p< 0.003.
Among the patients whose Height was > -2 SDS according to SP charts but ≤ - 2 SDS according to WHO standards, 7 had growth hormone deficiency (GHD), 2 had Turner syndrome (TS), 2 had Prader-Willi syndrome (SPW) and 15 were born SGA.
In group 2 (667 children, 53% boys, mean age: 10.3± 3.6 years):
The mean Height z-score wasn't significantly different for the two references (SP: -2.72±1.33, WHO: -2.83±1.14; p=0.11).
The percentage of children whose height for age z-score was < -2 SDS was higher using the WHO references (80%) compared to the French ones (73.2%), p< 0.003. Among the patients whose Height was > -2 SDS according to SP references but ≤ - 2 SDS according to WHO references, 9 had GHD, 5 had TS, 1 had SPW and 12 were born SGA.
Conclusions: The use of WHO charts seems to be more helpful for the screening of children with short stature.

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Linear growth of Indonesian children: growth declines and their association with parental height

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Background: Indonesian government is concerned for deficits in linear growth of the children.
Objective: To assess the association between parental height and the height of their children and the risk for growth decline in the first four years of life.
Methods: Subjects were 664 pairs of children (53.2% boys) with their parents in the municipality of Tangerang, Indonesia. They had their length measured at birth, at the age of 6-12 months and at the age of 3-4 years. Length and height were compared to WHO growth standard 2005. Parental heights were compared to WHO growth reference 2007 for age 19 years (considered as adult heights).
Results: At the age of 3-4 years, mean(SD) height SDS of the children was -1.44(1.31). Compared to length at birth, standard deviation scores (SDS) for subsequent length/ height were lower, mean difference (95%CI) -0.50 (-0.65;-0.34) at the age of 6-12 months and -1.05 (-1.23;-0.87) at the age of 3-4 years. However, compared to their parents, the children were still taller, mean difference (95%CI) 0.22 (0.12;0.33) with maternal height and 0.39 (0.28;0.50) with paternal height. The decline between the age of 6-12 months and the age of 3-4 years was correlated with maternal height (r=0.13, p=0.001), and not with paternal height (r=0.06, p=0.15).
Conclusion: Indonesian children lost more than 1 SDS in height during the first four years of life, although they were still taller then their parents. The decline was associated with maternal height.

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Early postnatal growth retardation as a first sign of progeria

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Background: Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare condition connected with the premature ageing. It is caused by dominant heterozygous mutations within the *LMNA* gene which encodes the lamins - proteins comprising the major structural components of the nuclear lamina. Lamins also compose the fibrous meshwork underlying the inner nuclear membrane.
Case report: The boy was born from second uneventful pregnancy at 39th week of gestation. His birth weight was 3270 g, birth length 46 cm (SGA). During infancy, he displayed delayed motor development, early closure of large fontanel, and markedly delayed dental eruption. At the age of 12 months, the failure to thrive and growth retardation (-2.6 SDS) was noted. The endocrine testing performed at the age of 20 months showed low level of the IGF1 (40 ug/L); the clonidine test proved insufficient stimulation of growth hormone (2.43 ug/L). The MRI showed empty sella. Therefore, the growth hormone replacement was started. The effect of this treatment was poor, the growth retardation progressed up to -3.0 SDS. In parallel, syndromic signs including the partial hair loss and thin skin suggesting progeria appeared. In proband we performed molecular genetic testing of the *LMNA* gene using direct sequencing. We identified a heterozygous base substitution within exon 2 (p.Glu145Lys) that was published previously in a single patient. All *LMNA* mutations causing HGPS described so far (including our patient) have been sporadic.
Conclusions: We described a boy with the growth retardation as a first sign of progeria. Prognosis of our patient is very poor, the median life expectancy with HGPS is 13 years and no therapy is available for those with p.Glu145Lys mutation.
The study was supported by the institutional grant from the Czech Ministry of Health (grant MZ NT13692).

P2-d1-994 Growth 6

Long-term efficacy and safety of recombinant human growth hormone (rhGH) in children with chronic kidney disease (CKD): a single-center experience

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Background: Growth failure represents a common and significant problem for children with chronic kidney disease (CKD) with a multifactorial etiology. Although growth hormone is usually adequately produced, treatment with rhGH is indicated in cases where growth remains suboptimal.
Objective and hypotheses: To assess efficacy and safety of rhGH treatment in children with CKD in our center.
Methods: Eleven short children (7 boys and 4 girls) with CKD and a mean decimal age of 8.36±4.06 years (range: 2.34-12.39 years) at the beginning of treatment with rhGH participated in this study. Three patients had undergone renal transplantation, 7 patients were requiring peritoneal dialysis and 1 patient was on CKD stage IV and not yet on dialysis. Anthropometric variables were assessed every 6 months and Z-scores were calculated according to sex and age matched population. Parental heights, medical history and other data were retrieved from patients' medical files.
Results: One patient died during the study of unknown cause. One other patient discontinued treatment after renal transplantation. All nine remaining patients are still on treatment with rhGH. Mean duration of treatment was 27.20±14.51 months (range: 12 - 52 months) with a mean dose of 0.034 mg/kg/d. Three patients discontinued treatment temporarily: one for transplantation, one due to increased levels of parathormone and one due to worsening of genu valgum. Height SDS - Target Height SDS at the beginning was -2.25±1.00, whereas at present it is -1.82±1.08 (p=0.06). All patients improved their height SDS except the patient who deceased and one patient who underwent transplantation, received corticosteroids and is on rhGH for only 15 months. Mean height velocity SDS improved significantly on treatment (-2.52±2.15 pre versus 0.87±1.43 after treatment, p=0.04).
Conclusions: A substantial improvement in height can be achieved with a favorable risk-benefit profile in CKD children receiving rhGH.

P2-d1-995 Growth 6

Short stature, complex cardiac defects and developmental delay associated with a *de novo* microduplication of chromosome 15q13.2q13

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Introduction: Microduplication of 15q13.2q13.3, a region that includes the gene encoding the cholinergic receptor nicotinic alpha 7 (*CHRNA7*), is associated with mild to moderate intellectual disability, autism, psychiatric disorders and epilepsy. Small stature, cardiac defects, or ovarian failure have not been described.
Case report: The 15-year-old female has a congenital complex left side heart defect (juxtaductal coarctation, hypoplasia of the aorta, arteria lusoria), dysmorphic stigmata (relative macrocephalia), radio-cubital subluxation, and global developmental delay. She has always been short (-2.4 SD); although her height was in line with predicted mid-parental height. Subsequently, she had a blunted pubertal growth spurt. Menarche occurred at age 12 followed by regular menses. Family history was negative for developmental or cardiac disorders.
On examination, she has dysmorphic features, is obese (BMI: +3.0 SD), Tanner V breast & pubic hair, and marked short stature (-4.77 SD, height:sitting-height ratio = 1.2). Biochemical testing revealed an IGF1 of 360 µg/l (235 - 930), LH 11.7 U/L, FSH 3.5 U/L, serum estradiol 1.36 nmol/L, Inhibin B 63.1 pg/mL (35-182--normal) and low AMH (6.9 pmol/L ; 5-800). Arginine stimulation testing at 7 years of age was normal (peak GH 10.1 µg/L).
Results: Karyotype was normal (46,XX). Array CGH (comparative genomic hybridization) (Agilent human genome kit 244 k) revealed a heterozygous *de novo* 1.58-1.8 Mb microduplication of 15q13.2q13.3, and a paternally inherited 389-518 kb microdeletion in 15q11.2.
Conclusions: Cardiac defects and short stature could be considered as new clinical features of the *de novo* duplication in 15q13.2q13.3 found in our patient.

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Familial 17 q23.3 deletion and Xp 22.31 duplication detected using array-CGH in a girl with Silver Russell phenotype

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Background: Silver-Russell Syndrome (SRS) is characterized by severe intrauterine growth restriction (IUGR), poor postnatal growth, relative macrocephaly, triangular face, asymmetry and feeding difficulties. Hypomethylation of the imprinting control region (ICR1) on chromosome 11p15 and maternal uniparental disomy (mUPD7) for chromosome 7 are found in up to 60% and in 5-10% of cases respectively, while no mutations are identified in 40% of SRS.
Case report: We investigated a 5-year-old girl with growth retardation, born at term from non consanguineous parents, with a length < 3rd centile (46 cm) and a weight adaptive for gestational age. The girl showed typical features for SRS such as triangular face, broad forehead and legs asymmetry. Her mother showed disharmonic short stature (146 cm), relative macrocephaly and strong facial features.
Methods: Polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) and array comparative genomic hybridization (array-CGH, Illumina 244K) were performed for DNA analysis.
Results: PCR and FISH analyses were negative for mUPD7 and hypomethylation defects; array-CGH revealed a maternally-inherited deletion in 17q23.3 and a duplication in Xp22.31.
Conclusions: A deletion in 17q24-25 has been reported in 3 cases of SRS; in this region the GH gene cluster comprising 2 GH genes (GH1 and GH2) and the somatomammotropin-like genes (CSH1, CSH2, CSH-L) has been localized. These 3 cases presented IUGR and a lack of postnatal catch-up growth, while our patient only showed a low birth length associated with other SRS features. The role of Xp duplication is not clear yet; females Xp duplication carriers have been described as normal; however the contiguity of this duplication to the short stature homeobox gene (SHOX) may explain the mother's disharmonic dwarfism. This study highlights the essential role of array-CGH in patients without mUPD7 or hypomethylation anomalies, in whom SRS is suspected on the basis of clinical features.

P2-d1-997 Growth 6

Early detection of celiac disease in children by using height and weight in screening

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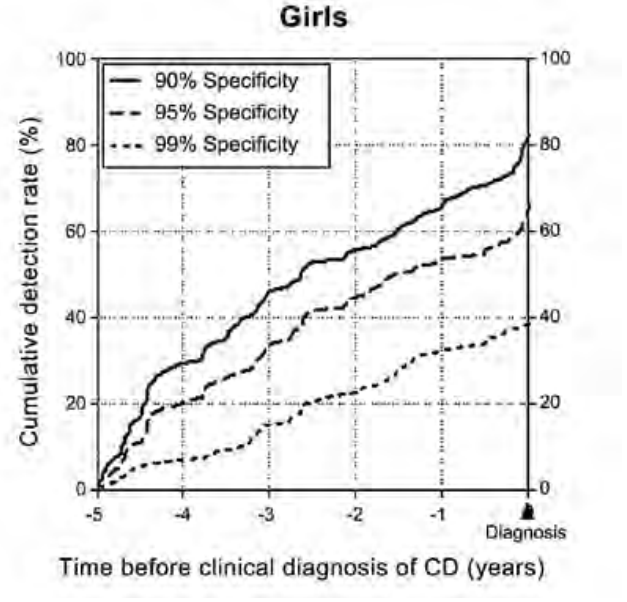
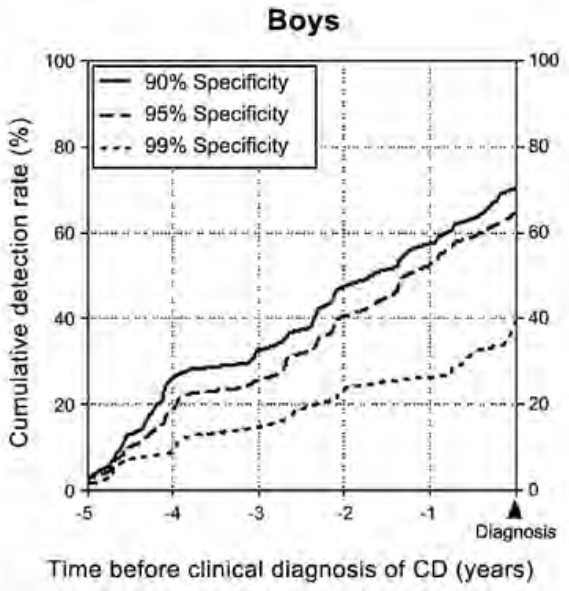
Background: Growth monitoring aims at early detection of disorders affecting growth. However, the diagnostic performance of the screening for celiac disease (CD) by using height and weight measurements is not well known.
Objective and hypotheses: To evaluate growth patterns in children with CD, and diagnostic performance of six growth parameters.
Methods: Growth of 177 CD children was evaluated. The following six growth parameters [height SDS and BMI SDS, distance from target height, change in height SDS or BMI SDS, and combination of these five] were evaluated against the reference population of 51,322 healthy children.
Results: At the time of CD diagnosis, mean (SD) height and BMI SDSs were -0.45 (1.08) and -0.25 (1.23) for girls and -0.58 (1.17) and -0.44 (1.08) for boys, respectively. CD was detected in good accuracy [Receiver Operating Characteristics AUC (95% CI) = 0.88 (0.84-0.93) for girls and 0.84 (0.77-0.91) for boys, respectively) when screening was performed in the combination rule. Growth was abnormal in 56.6% of the CD girls (Figure 1) and 47.9% of the CD boys (Figure 2) two years before the diagnosis, when the specificity was set at 90%. Detection rates at 95% and 99% specificities were 45.3% and 22.6% for the girls and 40.1% and 23.9% for the boys, respectively.



[Figure 1]



[Figure 2]

Conclusions: CD could be detected with good accuracy when several screening rules for abnormal growth were used at the same time. Some children with CD grew abnormally long before the diagnosis of CD was made and they could have been detected several years earlier by utilizing population-based growth monitoring program.

P2-d1-998 Perinatal and Neonatal Endocrinology 2

Congenital hyperinsulinism in an infant with paternal uniparental disomy on chromosome 11p15

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Background: Recently, epigenetic alterations of chromosome 11p15 have been detected in patients with no or few clinical features of Beckwith-Wiedemann syndrome (BWS). The underlying mechanism leading to congenital hyperinsulinism (HI) in BWS remains unclear. In the majority of BWS patients, hypoglycemia will be asymptomatic and resolve within the first few days of life. Less than 5% of patients will have hypoglycemia beyond the neonatal period.
Objective and hypotheses: We report an infant with diazoxide-unresponsive HI without any apparent clinical features suggestive of BWS, but diagnosed by molecular testing due to the somatic mosaicism of paternal UPD on chromosome 11p15.
Method: We first excluded mutations in the K_{ATP} channel genes on chromosome 11p15.1, but found a rare homozygous single nucleotide polymorphism (SNP) of *ABCC8*. Parental SNP pattern suggested paternal UPD in this region. To confirm paternal UPD, microsatellite marker analysis on chromosome 11p15 was done.
Results: The percentage mosaicism of paternal UPD was around 70 %.
Conclusions: Early diagnosis of BWS is particularly important because patients with BWS have a predisposition to embryonal tumors. Given that the genetic etiology is still unknown in nearly half of HI, some HI might be involved in undiagnosed BWS with no apparent clinical features.

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Cardiovascular fitness in prepubertal children born small for gestational age

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Background: Small for Gestational Age children (SGA) have an increased risk of developing cardiovascular and metabolic diseases in adulthood. Benefit of fitness to reduce the risk is well known.
Objective and hypotheses: Contrasting reports suggest that physical performance is impaired in SGA children. We aim to evaluate exercise performance and aerobic capacity in a group of SGA children compared with a control group of children born Adequate for Gestational Age (AGA).
Methods: We analyzed 22 SGA (male= 10, mean age 9.3±1.9) and 21 age and sex matched AGA children (male= 15, mean age 9.9±1). Glycemic and lipid profiles were estimated in SGA group. Insulin resistance (Homeostasis Model of Insulin Resistance, HOMA-IR) was estimated in SGA children. All children underwent maximal Cardiopulmonary Exercise Test (CPET) and Oxigen uptake (VO2 max). All values were normalized for age and sex (percentage of normal values).
Results: SGA children showed lower maximal time of exercise (TE, raw data and %) and oxygen consumption (VO2 max- l/min and %) during CPET compared to AGA.
Conclusion: Our preliminary data suggest that SGA children have lower physical fitness than AGA children.

P2-d1-1000 Perinatal and Neonatal Endocrinology 2

Immediate severe hyperglycaemia enables the differential diagnosis between transient idiopathic hyperglycaemia and neonatal diabetes mellitus in premature newborns

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Background: Transient Neonatal Diabetes Mellitus (TNDM) is a rare genetic form of pancreatic beta-cell dysfunction leading to hyperglycemia early in life and resolving in early childhood. Four main genetic causes were described: chromosome 6q24 abnormalities and mutations in *KCNJ11*, *ABCC8* and in the preproinsulin (INS) genes. Transient idiopathic hyperglycemia is often reported in very preterm infants and is usually related to defective processing of proinsulin and to insulin resistance.
Aim: To investigate the prevalence of TNDM in very preterm infants with hyperglycemia and to describe their phenotype.
Patients and methods: We selected newborns less than 32 weeks of gestation (WG) and who had glycemia more than 10 mmol//L, at least twice during the two first weeks of life, in a neonatology unit. Newborns with infection or organ failure were excluded. We recorded phenotype and glycemic profile, and investigated for alterations in the chromosome 6q24 region and for mutations in *ABCC8, KCNJ11* and *INS* genes.
Results: We included 15 newborns from 379 premature infants born less than 32 WG. We found a mutation in *KCNJ11* gene (F333S, n=1) and 6q24 abnormalities (n=1). As compared with non-mutated patients, TNDM patients had a higher glycemia during the first day of hyperglycemia (median 23.5 vs 13.5 mmol/l, p=0.03), and required a higher daily insulin dose (median 1.16 vs 0.24 unit/day, p=0.03). Insulin therapy was longer in the TNDM patients (median 85 vs 11 days, p=0.03) and was stopped at a median age of 39.3 WG vs 29.4 WG in non-mutated patients.

Conclusion: Idiopathic hyperglycemia of the very preterm infants may be linked in some cases to TNDM. Higher early hyperglycemia, higher insulin doses and unusual long duration of insulin therapy should ask for genetic testing for the known causes of TNDM. The identification of TNDM indicates an extended follow up during childhood and puberty due to the possibility of recurrence of glucose intolerance.

P2-d1-1001 Perinatal and Neonatal Endocrinology 2

Neonatal Wolfram syndrome: novel de-novo dominant mutation presenting as an unusual clinical phenotype

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Background: Wolfram, known also as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness) syndrome (WS) is a rare neurodegenerative disorder resulting usually from biallelic WFS1 gene mutations. Diabetes mellitus usually its first symptom, rarely presents prior to 1y of age.
Methods and results: Exome sequencing was performed on a 5.9 years old boy from a consanguineous Palestinian family. He presented neonatally at 40d of age with persistent neonatal diabetes, bilateral cataracts, congenital (prelingual) deafness and left hydronephrosis. During follow up he developed failure to thrive, microcephaly, severe psychomotor retardation, seizures, severe scoliosis and bilateral lower limbs contractures.
Laboratory investigations revealed normal serum electrolytes, lipase and thyroid function tests, normal urine osmolality, low serum insulin levels, negative anti insulin antibodies, normal pancreas by sonogram, 46,XY karyotype, and normal sequencing of the KiR6.2 gene.
Whole exome sequencing revealed a heterozygous, c.923 C>T (p. S308F) novel, de-novo, missense mutation in an evolutionary conserved amino acid of WFS1; that was defined damaging by predicting softwares.
Although wolframin 1's function has not been established its known formation as an oligomer suggests, that a dominant negative effect may cause the severe phenotype.
Conclusions: A novel de-novo heterozygous WFS1 mutation causes a unique and severe WS with cataracts, deafness and diabetes mellitus presenting **neonatally**. The clinical application of next-generation sequencing technology enhanced the diagnosis of a rare genetic disorder in a patient with atypical presentation and may have a role in defining new clinical manifestations of rare syndromes, such as WS.

P2-d1-1002 Perinatal and Neonatal Endocrinology 2

Intra-uterine growth restriction (IUGR) associates with more severe hyperinsulinaemic hypoglycaemia (HH) in children born small for gestation age (SGA)

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Background: Children born SGA may have hypoglycaemia due to dysregulated insulin secretion. However, the mechanisms for hyperinsulinism and the relationship to intra-uterine growth in SGA children are not clear.
Objective and hypotheses: To characterise a cohort with HH due to SGA, and assess if IUGR influences the severity of HH.
Methods: Children born SGA with a birth weight < -1.6 SDS were identified (n=20), if they developed HH by age 7 days. Children with perinatal asphyxia and genetic syndromes were excluded. IUGR was determined if 3rd trimester ultrasound scanning demonstrated sequential reduction in fetal growth parameters.
Results: There were 16 (80%) males in this cohort. Caesarean section was the delivery mode in 13 (65%) children. The median (range) birth weight SDS was -2.4 (-3.5;-1.7), with an insulin of 7.4 (2.5; 92.0) mU/l at hypoglycaemia and carbohydrate requirement (CHO) of 16.6 (10.8;22.0) mg/kg/min. No genetic mutation was identified. Diazoxide was used to treat hypoglycaemia in 18 (90%) children [maximum dose 5.0 (2.0;21.0) mg/kg/day], of whom 2 received second line octreotide. In all but 4 (20%) children, HH was self-resolving, but duration of treatment was often prolonged [150 (4;960) days]. A longer time to resolution correlated with greater diazoxide dose (R=0.8, p=0.002), indicative of the severity of HH. IUGR was present in 12 (60%) children, who required greater diazoxide dose [7.4 (5.0;21.0) v 5.0 (2.0;11.0), p=0.04] for a longer duration [365 (21;960) v 38 (4;365) days, p=0.03] than those without IUGR, with no correlation with maternal risk factors of smoking, antihypertensive use, body mass index, mode of delivery or other HH severity markers, such as glucagon treatment, seizure frequency and CHO requirement.
Conclusions: HH in SGA children occurs predominantly in males, usually requires medical therapy for several weeks, but is self-resolving in the majority. If IUGR is present, HH is likely to be more severe and last longer.

P2-d1-1003 Perinatal and Neonatal Endocrinology 2

The proportion of uniparental disomy is increased in Prader-Willi syndrome due to an advanced maternal childbearing age in Korea

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Background: Prader-Willi syndrome (PWS) is a genetic disorder caused by the absence of expression of the paternal copy of maternally imprinted genes in chromosome region 15q11-13. The genetic subtypes of PWS are classified into deletion (~70%), maternal uniparental disomy (mUPD; 25-30%), imprinting center defects (3-5%) and rare unbalanced translocations. Recently, Matsubara et al. reported a significantly higher maternal age in a trisomy rescue (TR) or gamete complementation (GC) by nondisjunction at maternal meiosis 1 (M1) group than in a deletion group.
Objective and hypotheses: In the present study, we try to confirm their findings in an ethnically different population.
Methods: A total of 97 Korean PWS patients were classified into deletional type (n=66), TR/GC (M1) (n=15), TR/GC by nondisjunction at maternal meiosis 2 (n=2), monosomy rescue or postfertilization mitotic nondisjunction (n=4), and epimutation (n=2).
Results: Maternal ages at birth showed a significant difference between the deletion group [median age of 29, IQR=(27,31)] and the TR/GC (M1) group [median age of 35, IQR=(31,38)] ($P < 0.0001$). The relative birth frequency of the TR/GC (M1) group has substantially increased since 2006 when compared to the period prior to 2005.
Conclusions: These findings support the hypothesis that the advanced maternal age at childbirth is a predisposing factor for the development of mUPD because of increased M1 errors.

P2-d1-1004 Perinatal and Neonatal Endocrinology 2

The safety and patterns of use of octreotide in the treatment of congenital hyperinsulinism

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Background: Congenital Hyperinsulinism (HI) is a rare disorder causing hypoglycemia and has a 20-40% chance of causing brain damage. There is one drug approved for use in this condition in the US, Diazoxide. Octreotide (Oct) is used off label to treat patients with HI. There is little safety data for this use and there have been concerns that necrotizing enterocolitis (NEC) may occur.
Objective and hypotheses: To describe drug use patterns and safety of Oct used in patients with HI.
Methods: A convenience sample was taken from 5 hospitals, looking at children treated with Oct for HI. The data was collected retrospectively by chart review on patients treated between Jan 2007 to Dec 2010.
Results: The data from 103 patients were reviewed, 3 Black, 1 Asian, 13 Hispanic, 52 White, and 32 Other, and 50.5% female. The median gestational age was 38 (28-40) weeks, N=84, and median birthweight was 3.73 kg (1.005-5.6), N=50. Median age at start of therapy was 15.2 (0.86-313.2) weeks, N=103. Two patients died during the hospitalization: one developed cardiorespiratory failure from cardiomyopathy present on admission, the other due to NEC occurring 3 days after Octreotide was started. 36/103 babies received partial pancreatectomies. There were 10 adverse events not followed by death, 3 hypoxia, 2 hyperglycemia, 1 DVT of the right basilica vein, 1 intussusception, 1 thrombosis at site of old line, 1 hypoglycemic seizure and 1 hypotension. Route of administration was SQ only (54), both IV and SQ (4), and IV only (45). The median total dose Oct (dose X administrations per day X days) was 62.7 mcg/kg (range 1.6 - 2625 mcg/kg). Median duration of therapy was 8 (1-84) days. Frequency of administration was QID (36), TID (29), BID (19), Qd (15).
Conclusions: In this series, there was a 1% rate of NEC after using Oct and a 2% rate of thrombosis. A prospective controlled trial is needed to obtain more information on efficacy and safety in this setting.

P2-d1-1005 Perinatal and Neonatal Endocrinology 2

"Crocodile" thyropathy in newborns: a novel cause of neonatal goiter with hypothyrosis

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Background: Neonatal goiter with hypothyrosis in newborns is a rare pathology caused by impairment of biosynthesis of thyroid hormones.
Objective and hypotheses: To describe neonatal goiter with hypothyrosis in newborns whose mothers during pregnancy used narcotic drug desomorphine.
Methods: We examined 6 newborns whose mothers were narcodependent and used the narcotic drug desomorphine called "Crocodile" among the narcodependent people. One dose of narcotic contains 2-3 g of iodine. In all newborns there were performed USI of thyroid gland, studies of levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), and anti-thyroid peroxidase antibodies (ATP-AB) in the blood serum.
Results: All newborns had a pronounced increase of thyroid causing a change of the neck contours. The TSH level in the whole blood was from 95 to 170 μU/ml. In the blood serum the TSH concentration varied from 77.3 to 114.5 μU/ml, the FT4 concentration - from the non-determined to 8.2 pmol/l. The ATP-AB was within the normal values. By data of the thyroid USI in all cases, the gland volume was increased and amounted from 4.2 to 13.3 ml, the echostructure was uniform, of intermediate echogeneity.To four newborns, sodium levothyroxine at a dose of 25-50 μg was prescribed. In all newborns including those who were not treated with levothyroxine, the sufficiently fast (for 2-3 weeks) normalization of the TSH and free thyroxine levels was observed. At the same time, although the sizes of thyroid decreased, but they did not reach normal values in any of examinees for 12 months of observation.
Conclusions: Use by pregnants of desomorphine ("Crocodile") due to its high content of iodine can lead to development in their newborns of goiter with hypothyrosis due to the well-known Wolf-Chaikov phenomenon. In revealing such cases, medical workers are recommended to elucidate the fact of use of this narcotic drugt during pregnancy.

P2-d1-1006 Perinatal and Neonatal Endocrinology 2

Neonatal waist circumference reference curves and its relationship with body mass index and ponderal index

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Background: Newborn size is a predicament for the increase of health problems risk of later life. Waist circumference and proxy measure of abdominal obesity are used to determine cardio-vascular risk factors in infancy and childhood.
Objective and hypotheses: The aim of this study was to present gestational age specific waist circumference for soothed reference curves in newborn infants and to determine relationship with body mass index and Ponderal index.
Method: This prospective study included preterm and term pregnancies within 2 year period. Inclusion criteria were a singleton pregnancy, absence of structural abnormality and chromosomal disorders. The anthropometric measurement of total 3485 singleton ('1674 boys and 1810 girls) live births born between 33 and 41 weeks of gestation was recorded. Body mass index and Ponderal index were calculated, and percentiles for all gestational weeks were produced using the LMS program.
Results: There were 1810 (52 %) boys and 1674 (48%) girls newborn infants included in the study. 22 % of the infants were preterm and 78 % were term newborns. Gestational age specific 5th, 10th, 15th, 25th, 50th, 75th, 85th, 90th and 95th percentile values were produced. The descriptive characteristics of collected data were presented as mean (SD: standard deviation) and median (Min-Max: minimum-maximum) to provide detailed information other than smoothed values. Mean WC values increased with age. There was a positive correlation between BMI, PI, weight and WC in each gestational age.
Conclusions: These gestational age-specific references will be of use in clinical practice and can further help research on newborn body shape. Additionally, we suggest that the data can be used for implications in newborns metabolic status in future life.

P2-d1-1007 Perinatal and Neonatal Endocrinology 2

The clinical and chromosome 11p15 imprinting defects study in Silver Russell syndrome

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Background: Silver Russell syndrome (SRS) is a genetic disease that is attributed to imprinting defects. This is the first study of Chinese children with SRS caused by chromosome 11p15 imprinting defects.
Objective: The goal of this study was to analyze the clinical features and the genetic imprinting defects of SRS. Then we learn their relationship between the phenotype and genotype.
Methods: 25 SRS cases diagnosed in Beijing Children's Hospital from 2006 to 2012 were studied for clinical informations. We used the methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) method to detect chromosome 11p15 imprinting defects.
Results: The 25 SRS cases included 17 males and 8 females ranging in age from 0.08 to 12.17 years. Clinical characteristics found in over 80% of the patients included
(1) small for gestational age (SGA) and postnatal growth retardation(mean HT SDS was -3.56);
(2) severely low BMI (mean BMI SDS was -2.10);
(3) skeletal malformation such as micromandible, triangular face, limb asym-

metry and fifth finger clinodactyly.
HT SDS/ mean bone age retardation was 3.04. Chromosome 11p15 imprinting defects were detected in 16 of the 25 patients. 6 had hypomethylation in chromosome 11p15 ICR1. 1 had chromosome 11p15 ICR1 hypomethylation and ICR2 hypermethylation. In another patient, the maternal chromosome 11p15 fragment was duplicated. There is relationship between the ICR1 hypomethylation and anisometry, p=0.046. Six patients had been treated with growth hormone (GH) for 3 to 24 months. Growth velocity ranged from 4 to 10.8 cm/year.
Conclusions: The prominently clinical features of SRS are growth retardation which is more severe than bone retardation, severely low BMI and triangular face, limb asymmetry. Chromosome 11p15 imprinting defects are the major genetic disturbance in SRS. A relationship exists between ICR1 hypomethylation and anisometry.

P2-d1-1008 Perinatal and Neonatal Endocrinology 2

A report of neonatal screening for phenylketonuria in the past 20 years in Chengdu

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Background: Phenylketonuria (PKU) is an autosomal recessive aminoacidopathy that lead to mental retardation if it was not timely treated.In Chengdu, neonatal screening of PKU started in1992, this report is good representative data from Western China.
Objective and hypotheses: The main purpose of the study was determining the prevalence of the PKU in chengdu neonates.
Methods: We analyzed the data of neonatal screening for PKU in Chengdu from January 1992 to December 2011 which were obtained from Chengdu Network of Neonatal Screening Center. The screening methods were bacterial inhibition assay and quantitative enzymatic assay in 1992 to 2001, but it was time-resolved fluoro-immunoassayt in 2002-2011.
Results: There were 2055244 newborns and 1119874 (54.49%) of them with screening test for PKU. The screening rate was increased year by year.In the 20 years,4461 newborns with positive results by initial screening test and 3863 (86.59 %) were recalled to take confirmatory test. There were 50 cases diagnosed as PKU with a prevalence of 1 per 22397. Only 3 cases of them were diagnosed as tetrahydrobiopterin deficiency (BH4D) and its prevalence was1per373291. The positive cases of initial screening in the second decade were much more than the first decade, but the prevalence had no statistical difference ($\chi 2=0.457, P>0.05$,table 1). There were 2 cases diagnosed in the previous10 years and 48cases in the later 10 years. This difference was considered to be related to the significant increase in screening rate and recalling rate in the later 10 years. Another reason was different tests methods.
Conclusions: The neonatal screening and recall rate is increasing stably during the past 20 years. The positive cases in the first decade were much more than the second decade. The PKU prevalence in Chengdu is higher than the national average level.

Years	Newborns	Screening rate (%)	Positive rate (%)	Recall rate (%)	Confirmed cases(n)	The prevalence
1992~2001	818851	10.93 (n=89500)	0.70 (n=629)	61.84 (n=389)	2	$2.23/10^{5(1:44750)}$
2002~2011	1236393	83.34 (n=1030374)	0.37 (n=3832)	90.66 (n=3474)	48	$4.66/10^{5(1:21466)}$

[Table 1]

P2-d1-1009 Perinatal and Neonatal Endocrinology 2

Miliaria rubra revealing systemic pseudohypoaldosteronism type 1

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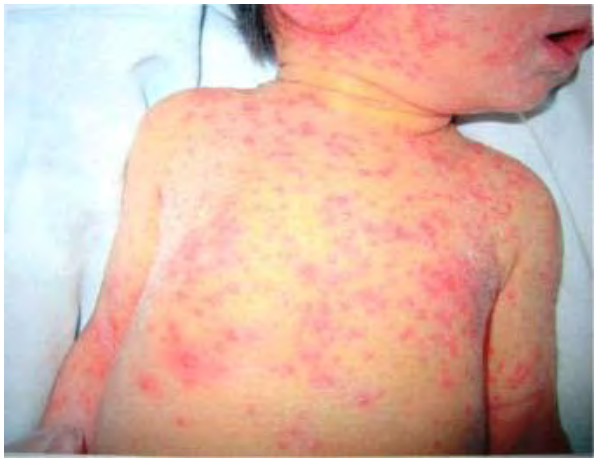
Background: Only few cases of neonatal miliaria rubra associated with systemic pseudohypoaldosteronism type 1 are described in literature.
Case study: We report the case of a full-term male newborn, from consanguineous parents. At his third day of life he presented a miliaria rubra.



[miliaria rubra]

The first hypothesis was an infection, but the cutaneous evolution was pejorative despite the antibiotics, with also weight loss and severe dehydration, metabolic disorders such as hyponatremia (112 mmol/L), hyperkalemia (10.1 mmol/L), and concomitant abnormal heart rhythm (ventricular tachycardia). Resuscitation and symptomatic treatments saved the newborn, and pseudohypoaldosteronism was diagnosed secondarily with very high levels of aldosterone (223000 pmol/L) and renin (13366 pg/ml). Afterwards, this newborn was orally treated with sodium polystyrene sulfonate (1 g / 4 hours), sodium chloride 20% (2.5 ml / 4 hours), sodium bicarbonate 4.2% (4 ml / 4 hours), and acetylsalicylic acid (50 mg / day). Homozygous mutation in the SCNN1B gene was identified in the newborn, and both parents that were cousins had the same heterozygous mutation. It confirmed systemic severe form of pseudohyopaldosteronism type 1.
Conclusions: This way of revelation by severe neonatal miliaria rubra is exceptional. It is linked to a defect of the epithelial sodium-channel responsible for increased sodium concentration in sweat. The boy, now aged 6 years old and still treated the same, still has a very dry skin.

P2-d1-1010 Pituitary and Neuroendocrinology 3

A novel homozygous *LHX4* mutation associated with severe panhypopituitarism leading to neonatal death

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Background: LHX4 encodes a member of the LIM-homeodomain transcription factor protein family that is required for development of the pituitary gland. To date, only heterozygous mutations in LHX4 have been associated

with variable combined pituitary hormone deficiencies (CPHD).
Objective and hypotheses: To investigate a cohort of patients with congenital hypopituitarism for mutations in LHX4.
Method: We screened 150 patients with CPHD (the vast majority having an ectopic posterior pituitary (EPP)) using PCR and direct sequencing analysis. Upon identification of any variants, 100 ethnically-matched controls were screened and control databases (1000 genomes, dbSNP) consulted.
Results: We identified a novel homozygous missense mutation (c.377C>T, p.T126M) in two deceased male patients of Pakistani origin, born to non-consanguineous parents, with panhypopituitarism. The parents also had a daughter with a depressed nasal bridge and cleft palate. The second son had panhypopituitarism and was born small for gestational age with a micropenis, underdeveloped scrotum, and mid-facial hypoplasia. In spite of rapid commencement of hydrocortisone and thyroxine, all three children died within the first week of life. DNA analysis confirmed the presence of a homozygous p.T126M mutation, located in the LIM zinc-finger binding domain 2, predicted to alter protein-protein interaction. Additionally, we identified a novel heterozygous missense mutation (c.1009A>C, p.N337T) in a Caucasian female patient with isolated GHD (peak GH: 1.47ng/µl) learning difficulties, obesity and an EPP. The mutation is in the C-terminal domain, possibly affecting protein folding. Both mutations are located at highly conserved residues. Functional studies are currently underway.
Conclusion: We report for the first time to our knowledge a novel homozygous mutation in LHX4 associated with a lethal phenotype; recessive mutations in LHX4 may be incompatible with life in the majority of cases.

P2-d1-1011 Pituitary and Neuroendocrinology 3

Development of multiple pituitary hormone deficiencies (MPHD) in paediatric patients originally diagnosed with isolated GH deficiency (IGHD) of organic aetiology

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Background: Pts with initial organic IGHD diagnosis may develop additional (add'l) pituitary hormone deficiencies (PHDs).
Objective: To identify factors predicting development of MPHD & determine the time course.
Methods: During follow-up (f-u) of 716 pts with organic IGHD in the GeNeSIS observational study, newly diagnosed PHDs were ascertained using case report form check boxes, adverse event reports, or start of replacement therapy.
Results: For the total cohort ≥1 add'l PHD was reported for 71/716 pts (10%) during mean±SD f-u of 3.3±2.9 years (y). Limiting analysis to pts with ≥3.5 y f-u or development of MPHD in < 4.5 y (4 y cohort; f-u 5.8±2.3 y) ≥1 add'l PHD was reported for 60/290 (21% overall; 27/80 [34%] with acquired GHD, 33/210 [16%] with congenital GHD). Reported deficiencies were TSH 73%, LH/FSH 23%, ACTH 15% & ADH 10%. During 4.5 y f-u 1 add'l PHD was reported for 80%, 2 for 18% & 3 for 2%. Compared with pts who remained IGHD, those who became MPHD were older at GHD diagnosis & GH initiation, but had lower baseline IGF-I SDS & GH peak (Table).

Variable (mean ± SD, unless stated)	Developed MPHD	Remained IGHD	P-value (ANOVA)
Age at diagnosis of GHD (y)	8.2 ± 4.4	6.8 ± 3.7	0.017
Age at start of GH (baseline; y)	9.0 ± 4.3	7.4 ± 3.6	0.005
Baseline IGF-I SDS	-4.4 ± 2.1	-2.9 ± 2.1	0.007
Maximum stimulated GH peak (median [Q1, Q3]; µg/L)	1.6 [0.6, 3.3]	4.9 [2.7, 7.9]	<0.001
Follow-up time (y)	5.5 ± 2.8	5.9 ± 2.2	0.196

[Pts who became MPHD vs. remained IGHD (4 y cohort)]

In the full cohort, time (y) from diagnosis of GHD to 1st add'l PHD [median (Q1;Q3)] was 1.0 (0.9;2.3) for ADH, 1.9 (1.7;2.8) for ACTH, 2.4 (1.0;3.6) for TSH & 6.0 (2.5;7.3) for LH/FSH. Multivariable logistic regression identified female sex, older baseline age, longer f-u, & lower GH peak as significant predictors for development of MPHD.
Conclusions: Pts with organic IGHD, especially severe &/or acquired GHD have high risk of developing MPHD. However, even after 4 y of observation 79% of pts had not manifested add'l PHDs. As symptoms of add'l PHDs may be delayed, long-term monitoring of pituitary function is recommended.

P2-d1-1012 Pituitary and Neuroendocrinology 3

Impact of athletic activity vs. hypogonadism on regional body composition, haemodynamic and haematological parameters, and liver function tests

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Background: Low weight with amenorrhea, as in anorexia nervosa, is characterized by changes in body composition, liver function tests (LFTs), hemodynamic and hematologic parameters, likely markers of malnutrition. The impact on these parameters of athletic activity in normal-weight adolescents (+/- amenorrhea) has not been defined, and is important because of clinical implications.
Objective and hypotheses: We examined the impact of athletic activity with or without hypothalamic amenorrhea on body composition, LFTs, hemodynamic and hematological parameters.
Methods: We examined vital signs, a blood count, LFTs and regional body composition (using DXA) in 46 amenorrheic athletes (AA), 24 eumenorrheic athletes (EA) and 23 non-athletes (NA) 14-21 years old. Subjects were normal-weight; athletes were weight-bearing endurance athletes.
Results: Groups did not differ for age, bone age or height. BMI was lower in AA than EA, and did not differ from NA. Menarchal age was lower in AA than the other groups. Systolic BP and pulse pressure were lowest in AA, and lower than in EA. Heart rate (HR) was lower in athletes than NA. Temperature was lower in AA than EA and NA; blood counts did not differ. AST was higher in athletes vs. NA, while ALT was higher in AA vs. EA and NA. Total, trunk and extremity fat were lower in AA vs. EA and NA, and % body fat lower in athletes vs. NA. Total and extremity lean were higher in EA than NA. Percent trunk and extremity fat and % extremity lean mass did not differ. Total, trunk and extremity fat, and % body fat were associated positively with HR and inversely with AST and ALT. Total and extremity lean mass correlated inversely with HR, and positively with AST (but not ALT).
Conclusions: Athletic activity is associated with lower HR, higher AST, and lower %body fat; hypogonadism is also associated with lower systolic BP, higher ALT, and lower total and regional fat. The latter are associated positively with HR and inversely with ALT/AST.

P2-d1-1013 Pituitary and Neuroendocrinology 3

Significance of PSIS diagnosis in the management for GHD patients

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Objective and hypotheses: To analyze the significance of pituitary stalk interruption syndrome (PSIS) diagnosis in the management of growth hormone deficiency (GHD) patients.
Methods: Three hundred and two GHD patients were recruited in the study. Those with acquired pituitary diseases were not included. Subjects were divided into two groups. Boys who were older than 13 year-old and girls older than 12 year-old were defined as old-age group, serum levels of the GH, TSH, ACTH, FSH and LH were evaluated for the group. Those boys who were

younger than 13 years old and girls younger than 12 years old were defined as young-age group, GH, TSH, and ACTH were evaluated for them.
Results: There were 66 (21.85%) GHD patients with PSIS (53 boys, 13 girls) out of 302 GHD children who were carried out MRI scans of pituitary. Of the 66 PSIS patients, 39 in old-age group, aged (16.27±5.10) years old (34 boys, 5 girls); 27 in young-age group, aged (9.23±2.45) years old (19 boys, 8 girls).The rest 236 GHD children were those with normal pituitary or with other kinds of congenital pituitary aplasia. There were statistically significant difference between the medians of the GH peak of the PSIS group and non-PSIS group (0.373μg/L vs 5.01μg/L, p< 0.01). The incidence of multiple pituitary hormone deficiency (MPHD) in GHD patients with PSIS were significantly higher than that in GHD patients with non-PSIS (P<0.01) for both old-age group and young-age group. In the old-age group, there are 48.72% patients developed adrenal insufficiency, which was much higher than that in the young-age group (48.72% vs 22.22%,p< 0.01).
Conclusions: High prevalence of PSIS was found in GHD patients. The extent of growth hormone deficiency were much more severe in the patients with PSIS than those with non- PSIS. GHD patients with PSIS should be evaluated for their pituitary functions, and further following-up is clinically important for the early diagnosis of the other anterior pituitary hormone deficiencies.

P2-d1-1014 Pituitary and Neuroendocrinology 3

Septo-optic dysplasia (SOD): clinical, endocrinological and neuroradiological phenotype

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Background: SOD is characterized by: optic nerve hypoplasia (ONH); midline brain defects-MBD- (agenesis-A-of septum pellucidum-SP-and/or corpus callosum-CC-); pituitary abnormalities
(anterior hypoplasia-ADH-,ectopic posterior pituitary-EPP, pituitary stalk abnormalities-PSA-) with hormone defects -HD- (combined/isolated pituitary hormone defects -CPHD/IPHD-). Conventional Magnetic Resonance (CMR) identifies CNS phenotypes; MR-biometry (MRB) is applied to study brain structures size.
Objective: Categorize MRI phenotypes;evaluate hindbrain MRB; correlate clinical and MRI features.
Methods: 38 patients (21 males, median 5.2yrs) were studied by CMR based on MBD identifying 3 subgroups (SG): IASP, IIACC, III presence of SP/CC combined to ONH and EPP; based on hindbrain CMR features they were stratified in GroupA (n=21 abnormal) and GroupB (n=17 normal). Patients and 119 controls (GroupC) were than studied by MRB (antero-posterior-AP, cranial-caudal-CC measure of mesencephalon-M, oblungata medulla-B, vermis-V and pons-P; APM/APP and M/P ratios). Biometric parameters were analyzed by ANOVA test (Kruskal-Wallis test corrected by Bonferroni-P_B) in the 3 groups (A, B, C) and clinical variables (CPHD, IPHD, developmental delay-RPM-, visual impairment, epilepsy) by X^2 test (Fisher's exact test, FET) in groups A, B and in the 3 SG.
Results: Group A showed reduced hindbrain biometric size compared to Group C (APP, CCP, APB, all PB's < 0,0001 and CCV, PB=0,009) and Group B (CCP and APP, PB=0,028 and 0,012, respectively); M/P was increased in Group A compared to Group B and C (PB< 0,0001). Hindbrain abnormalities were associated to SG IIACC (100%, p=0.002) while CPHD/IPHD (66.7%, p=0.005) to SG IIISP/CC. RPM (50%, P=0.012) was present in SG IIACC compared to other SG and in Group A compared to Group B (70.6%, P=0,035).
Conclusions: CPHD has a peculiar phenotype (ONH, EPP, ADH, PSA). SP and CC were not "protective" for HD when associated with ONH and EPP. RPM is common in a SOD subset of patients with small hindbrain size.

P2-d1-1015 Pituitary and Neuroendocrinology 3

Long-term weight development and psychosocial status in childhood craniopharyngioma patients

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Background: Craniopharyngioma (CP) are the most common sellar tumors in children. Patients often develop excessive weight gain and obesity due to several factors as involvement or damage of the hypothalamus. Previous studies on the weight development in craniopharyngioma patients have shown an increase in weight before and in the first ten years after diagnosis leading to an impaired quality of life. The long-term weight development in these patients has not been investigated till now.
Methods: In a retrospective study, we analysed the weight development of 108 craniopharyngioma patients who were diagnosed before 2001. Data from physical examinations, anthropometric measurements and the patient's records were used, as well as a questionnaire answered by the patients in 2011 on their current weight and psychosocial status. The BMI of CP patients at diagnosis, 8-12 years after diagnosis, during long-term follow-up and at the time they answered the questionnaire was analysed and factors were investigated for their effect on the weight development.
Results: Long-term survivors of CP were assessed at a median age of 26.1 years (range 14.8-42.7) after a median follow-up of 17.01 years (range 8.81-33.40) after CP diagnosis. All patients show an increase in BMI during the first ten years after diagnosis, as previously published. However, during long-term follow-up (more than 12 years after diagnosis) no further weight increase is seen. Patients with hypothalamic involvement of CP develop a higher initial weight increase, but also a stabilisation of BMI as well. Patients with a normal BMI at diagnosis (-2 to +2SD) show the highest weight increase during the first ten years after diagnosis, whereas patients presenting with obesity at diagnosis (BMI>3SD) show a smaller increase in BMISDS during long-term follow-up.
Conclusion: We conclude that the degree of obesity in CP reaches a certain plateau during long-term follow-up.

P2-d1-1016 Pituitary and Neuroendocrinology 3

Serum prolactin concentration in children with coeliac disease and role of gluten free diet: a longitudinal study

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Background: Celiac disease (CD) is a gluten sensitive autoimmune disease involving humoral and cellular immune pathways. Prolactin (PRL) has an immune stimulatory effect and promotes autoimmunity. Increased levels of PRL have been described also in CD but few data from cross-sectional studies are available.
Objective and hypotheses: We aimed to evaluate PRL secretion in CD patients at diagnosis and during the gluten free diet (GFD), only if increased at CD diagnosis.
Methods: We recruited 78 newly diagnosed and otherwise healthy patients (25 males; age 6.2 +/- 4.0 yrs) and 33 control subjects age- and sex- matched. PRL was assayed by chemiluminescence methods before GFD and, if above 25 ng/ml at baseline, after six months of GFD.
Results: In CD patients, serum PRL was higher than in the controls (13.4 +/- 8.7 vs 7.6 +/- 3.2 ng/ml, respectively, p < 0.001) and significantly decreased with age (Paerson's correlation coefficient = -0.27; p = 0.017). Seven patients (9%) showed a PRL level above 25 (ranging from 26.5 to 46) ng/ml. After 6 months of GFD, PRL decreased (range: 6.1 - 24.7 ng/ml) and anti-transglutaminases antibodies became negative in all these 7 patients.
Conclusions: Our data confirm, in the largest sample ever recruited, that PRL is increased at diagnosis of CD as compared to healthy subjects. The original

finding of this study is that increased levels of PRL at diagnosis decrease during the GFD, getting normal after 6 months and with negative anti-transglutaminases antibodies. Our finding supports the hypothesis that PRL is involved in the mechanisms underlying CD and show that high levels of PRL disappear after 6 months of GFD. PRL may be considered a marker of autoimmune disease activity.

P2-d1-1017 Pituitary and Neuroendocrinology 3

Thiazide diuretic treatment of neonatal central diabetes insipidus

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Introduction: Central diabetes insipidus (DI) is notoriously difficult to manage in neonates. Serum sodium (sNa) levels fluctuate widely with DDAVP (desmopressin) therapy. Use of oral thiazide diuretic in combination with low solute feed is a standard treatment for nephrogenic DI. The ease of titration and administration of a thiazide makes it an attractive alternative to DDAVP therapy for neonatal central DI.
Case series: Table 1 compares DDAVP and vasopressin infusion to thiazide diuretic treatment in three cases of neonatal central DI.

	Case 1	Case 2	Case 3
Gestational age	Term neonate	27 week premature neonate	33 week premature neonate
Aetiology of central DI	Septo-optic dysplasia Panhypopituitarism	Isolated central DI (MRI normal	HSV encephalitis-related central DI
mean sNa (±SD) mmol/L - subcutaneous DDAVP	141.1 (± 6.6)	148.0 (± 5.9)	152.0 (± 7.5)
mean sNa (±SD) mmol/L - oral DDAVP	136.9 (± 6.1)	144.0 (± 6.1)	-
mean sNa (±SD) mmol/L - Vasopressin infusion	-	-	140.5 (± 5.2)
mean sNa (±SD) mmol/L - Hydrochlorothiazide	136.2 (± 3.9)	145.0 (± 3.2)	145.2 (± 2.1)
Hydrochlorothiazide dose	2 mg/kg/day	3 mg/kg/day	3 mg/kg/day
Total daily fluid intake during thiazide therapy	160 ml/kg low solute formula (no additional free water)	200 ml/kg - 150 ml/kg low solute formula, 50 ml/kg free water	200 ml/kg - 140 ml/kg expressed breast milk, 60 ml/kg free water

[Table 1]

Conclusion: In this case series, combined thiazide diuretic and low solute feed resulted in less variability of serum Na compared to other available treatments. Thiazide diuretics should be considered a viable alternative to DDAVP treatment in neonatal central DI.

P2-d1-1018 Pituitary and Neuroendocrinology 3

Male prolactinomas in the paediatric population

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Male prolactinomas are very rare. Paediatric forms are even rarer, only anecdotic cases have been reported. Our aim is to analyze their frequency and their characteristics.
Subjects and methods: The studied population is composed of children (≤16), adolescents (≤ 20) and older subjects suffering from lack of pubertal development due to pituitary tumour secreting prolactin. In this retrospective study (1980-2012) we have analyzed clinical, biological and radiological characteristics.
Results: Among 82 male prolactinomas we observed 14 boys or adolescents = 17 %. Mean age= 18± 6 years (15 -27). 4 were diagnosed before 16 (28.5%). The consultation was motivated by visual troubles, lack of pubertal development, and severe neurological troubles. Ophthalmological abnormalities were observed in 21.52%, overweight in 29%, galactorrhea with or without gynecomastia in 28.57% and lack of pubertal development in 50%. Pituitary tumours were all >1cm. Mean tumour height= 25.32mm (15-65.5mm), 3 (21%) were giants (≥40mm). Prolactin=3569.51ng/ml (124- 22728). Gonadal deficit was present in all cases, mean testosterone= 3.78nmol/l. Other pituitary deficits were also observed, even the posterior one. The tumour reached the chiasmatic area in all cases and was invasive in 71.42%. Severe neurological complications such as convulsions, meningitis, memory troubles were noted in 21.4%.
Conclusion: Paediatric male prolactinomas account for 17%. They are diagnosed late as only 4 were diagnosed in childhood. All were macro tumours and ¼ were invasive and/or giant which explains severe neurological complications.

P2-d1-1019 Pituitary and Neuroendocrinology 3

Anterior pituitary gland aplasia: neuroradiological, phenotypical and hormonal evaluation

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Background: Anterior pituitary gland aplasia (APA) is a rare disorder and only few case are reported in literature. Abnormalities in Magnetic Resonance (MR) as small or truncated stalk and ectopic posterior pituitary (EPP), various clinical features and different hormonal settings are described. APA is often associated with other midline defects as cleft lip and palate, choanal atresia or stenosis, solitary maxillary central incisor, agenesis of the septum pellucidum or corpus callosum. In many cases the genetic defect is still unknown; seldom genes regulating pituitary gland development are involved.
Objective and hypotheses: Evaluate neuroradiological, phenotypical and hormonal presentation of children affected by APA.
Population and/or methods: Four patients affected by APA (F, 2-10 yrs).

	CM	MG	MA	PS
Birth W SDS	-0,64	0	-0,17	0,75
Birth L SDS	-0,31	-0,31	-0,96	N.A.
Phenotype	frontal bossing, depressed nasal bridge, choanes stenosis and solitary maxillary central incisor	frontal bossing, depressed nasal bridge, solitary maxillary central incisor and low ear setting	frontal bossing, depressed nasal bridge, choanes stenosis, low ear setting and hexadactyly	frontal bossing, depressed nasal bridge, cleft palate and bifid uvula
Cortisol (ng/ml)	17	10	14	35
TSH (mcU/ml)	0,18	<0,01	0,08	0,13
GH (ng/ml)	0,1	<0,1	0,1	0
MRI	APA, EPP	APA, thin pituitary stalk	APA, EPP, pituitary stalk aplasia	APA, EPP, carotid artery aplasia
Genetic Analysis	SHOC2 neg	HESX1, PROP1, PIT 1 neg	POUF1, PROP 1, HESX1, LHX3 neg	HESX1 neg
Delta H/ midparental H SDS	-0,55	-1,79	-0,84	-1,58

*[**Results:** features of patients affected by APA]*

Conclusions: All our patients affected by APA present multiple pituitary hormone deficiency, with different phenotypical and neuroradiological settings, even if some common features are present. No mutations in the genetic analysis have been found. Therefore a larger sample of patients must be evaluated to better define the relationship between neuroradiological, phenotypical and hormonal aspects, in order to find possible new genetic mutations involved.

P2-d1-1020 Pituitary and Neuroendocrinology 3

Evaluation of pituitary function after infectious meningitis in childhood

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Background: Hypopituitarism may have different causes, amongst which infectious diseases of the central nervous system (CNS). Indeed, hypothalamic-pituitary dysfunction and especially isolated corticotropic insufficiency has been reported in as much as 20% of adults after mild and moderate infectious of the CNS. Few data on this topic, apart from isolated case reports, are available in children.
Objective and hypothesis: To determine the incidence and the clinical impact of pituitary dysfunction in children with previous diseases of the CNS of different etiologies.
Population and methods: Basal and stimulated (ACTH 250 mcg) pituitary function as well as anthropometric parameters (height, weight, pubertal status) were evaluated in 14 children (6F-8M, age 6.4±4.4 yrs, range 1.2-13.9 yrs) with previous infectious meningitis of different etiologies. The mean interval from the acute event was 17.6±10 months (range 3-32 months).
Results: All the subject had normal stature (mean height SDS 0.7±1.0), normal IGF-I (mean SDS -1.0±0.6), prolactin, ACTH, TSH and free thyroid hormones levels. Gonadotropin and gonadal steroids were concordant to pubertal status in all patients. Cortisol response to ACTH 250 mcg stimulation test was normal in all children (mean cortisol peak 30.4±5.8, nv 18 mcg/ml).
Conclusion: Hypopituitarism following infectious meningitis seems not frequent in childhood as observed in adults. These data are similar to those observed after traumatic brain injury, and may suggest that children pituitary may be less vulnerable to vascular and/or traumatic damages. Nonetheless, prospective longitudinal studies are necessary to understand the natural history of pituitary dysfunction after CNS infectious.

P2-d1-1021 Pituitary and Neuroendocrinology 3

Craniopharyngioma: clinical, metabolic and auxological evolution

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Background: Craniopharyngioma is a rare cancer with low grade malignancy but with high morbidity.
Objective and hypotheses: Study the trend in BMI after surgery and the risk factors for its increase. To estimate the effects of growth hormone on height prognosis and metabolic benefits. To verify whether the hypothalamic etiology of obesity is a risk factor for metabolic complications and the difference between essential and hypothalamic obesity.
Methods: Analysis of 16 patients (7 M and 9 F, average age 14.7 ± 4.6 years), periodically evaluated for auxological and radiological aspects; comparison of 9 obese patients to as many obese controls matched for age, gender and BMI.
Results: Diagnosis had been made by MRI at a distance median of six months from symptoms presentation. Surgery was done at a median distance of 27 days from the diagnosis. After surgery 100% of patients had ACTH deficiency, 94% ADH, GH and TSH. At the time of the operation the median BMI was 0.89 SDS. During the first year BMI increased of 0.41 SDS and was 1.28 SDS in the second year. The increase in BMI from the operation to the second year was statistically significant (p 0,05). A reduction in basal metabolic rate measured by indirect calorimetry was also observed but wasn't statistically significant compared to essential obesity. Growth hormone therapy increased growth rate at one and two years.
After two years of GH treatment total cholesterol was reduced from pathological average values to normal range. There were no significant differences in the prevalence of metabolic syndrome and hepatic steatosis between the two groups.
Conclusions: This study confirms that patients tend to increase in weight and underlines the role of reduced basal energy comsumption in craniopharyngioma etiology. Growth hormone therapy is effective not only for catch up, but also for the metabolic aspect.

P2-d2-1022 Pituitary and Neuroendocrinology 4

Evaluation of hypothalamic-pituitary function in children following acute bacterial meningitis

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Objective and hypotheses: Previous studies in adults and case reports in children have shown increased frequency of hypothalamo-pituitary dysfunction after infectious diseases of the central nervous system.The aim of this study was to evaluate the function of hypothalamo-pituitary axis in children with a history of bacterial meningitis.
Methods: Patients diagnosed with bacterial menengitis between April 2000 and June 2011 were included. Baseline and stimulated hormonal tests were performed as required for hormonal evaluations following a diagnosis of meningitis.
Results: Pituitary function was assessed following a period of 8-135 months (mean 53 months) after bacterial meningitis. Thirty-seven cases (27 male, 15 pubertal) with mean age of 11.1±4.4 years were included. Mean height SDS was 0.01±1.07 and mean BMI SDS was 0.543±1.15, all patients had a SDS above -2SD. Baseline cortisol and low dose ACTH stimulation revealed normal adrenal functions in all patients. Gonadotropin deficiency was not detected in any of the pubertal cases. Four cases (10.8%) had low IGF1 and IGFBP3 z-scores (< -2SD) according to age, sex and Tanner stage, but peak GH response in clonidine test was >10 ng/ml in 3 of them suggesting neurosecretory dysfunction of GH in these cases. The fourth case has died before the test. No one had TSH deficiency and diabetes insipitus, only one case had mild hyperprolactinemia.
Conclusions: This is the first systematic study which evaluated hypothalamo-pituitary function in detail in children with a history of bacterial meningitis. Our findings suggest that hypothalamo-pituitary dysfunction is not as common in childhood as in adulthood. The most remarkable finding was neurosecretory dysfunction of GH in some cases.

P2-d2-1023 Pituitary and Neuroendocrinology 4

Screening for POU1F1 mutations among Bulgarian patients with congenital hyposomatotropism

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Background: POU1F1 (PIT1), a pituitary specific transcription factor plays a key role in late pituitary differentiation, development and hormone expression. Mutations of the PIT1 gene cause congenital combined pituitary hormone deficiency (CPHD) including growth hormone (GH), thyrotropin and prolactin and are associated with anterior pituitary hypoplasia. Earlier studies in Bulgarian patients with congenital CPHD showed an allele frequency of PROP1 mutations in 12.2%.
Objective and hypotheses: To implement the PIT1 mutational screening as a diagnostic tool in congenital CPHD in order to assess the overall allele frequency of PIT1 mutations in Bulgarian patients with hyposomatotropism.
Study population and methods: 49 patients, all negative in the PROP1 screening, aged (x±SD) 7.7 ±4.4,(median 7.0) yrs, 15 females (7.3±3.9, median 6.4 yrs), 34 males (7.7±4.4, median 7.0) yrs.
Inclusion criteria: obligate congenital GH deficiency; additional criteria: CPHD and anterior pituitary hypoplasia (MRI&CAT scan); therefore phenotype characterization based on: auxology, bone age, hormonal tests (GH, TSH, fT4, Prl, LH, FSH, T, E2 by Delfia ®, IGF1&BP3, cortisol, AMH, Inhibin B by

ELISA); Molecular genetic analysis by direct sequencing of PIT1, exons 1-6.
Results: No mutations of PIT1 in the selected patients could be verified.
Conclusions: Congenital CPHD due to PIT1 mutations seems to be not as frequent as PROP1 mutations in Bulgarian patients. Therefore, the PROP1 mutational screening should preceed the PIT1 in younger patients with congenital CPHD.
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Endocrine problems in children with neurofibromatosis type 1

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Background: Neurofibromatosis type 1(NF1) is one of the most common autosomal dominant multisystem disease. Many of the endocrine problems especially related to puberty and growth may accompany NF1.
Objective and hypotheses: We evaluate growth, pubertal development and endocrine problems of patients with NF1.
Methods: We obtained anthropometric variables, clinical and laboratory data of 38 patients (18 girls and 20 boys), with sporadic (55.3%) or familial NF-1 (44.7%, 6 affected mothers and 11 affected fathers). The mean age at referral was 10.8±4.4 years (range 2,10 to 19 years) and 24 patients were pubertal (63.2%). The average age at diagnosis was 6.6 years and the mean follow-up period was 4.2 years.
Results: Short stature was recognized in 11 of the 38 children (28.9%). One of them had endocrine disorder (hypothyroidism). Obesity was diagnosed in 5 cases (13.2 %) and 5 cases were overweight (13.2%). Insulin resistance was detected in an overweight girl. Puberty was abnormal in 7/38 of the children (18,4%). Two delayed puberty, 1 central precocious puberty (1 male with optic glioma), 1 premature telarche, 2 premature pubarche and 1 pubertal gynecomastia were determined. Lisch nodules were seen in 9 cases (23.7%). Scoliosis was diagnosed in 5 cases (%13.2). Hypothyroidism were detected in 3/38 (7.9%) of the children. Two of them had autoimmune thyroiditis and one of them with congenital hypothyroidism (dishormonogenesis). The frequencies of vitamin D deficiency and insufficiency were 44.7 % and 10.5% respectively in winter. There are no sufficient vitamin D levels in our NF1 patients.
Conclusions: Vitamin D deficiency, obesity, short stature and pubertal disorders are the most common endocrine problems in our study group. We suggested that patients with NF1 should be consulted with an endocrinologist periodically.

P2-d2-1025 Pituitary and Neuroendocrinology 4

Endocrinopathies in beta-thalassemia major: evidences from ten years of follow-up and evaluation of combined iron chelation therapy

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Background: Endocrine and metabolic abnormalities are common in patients with b-thalassemia mayor (TM). Preventing comorbidities is important for these individuals who need life-long multidisciplinary care and treatment.
Objective and hypotheses: Evaluate the incidence and prevalence of endocrinopathies and evaluate the reversibility of endocrinopathies according to the modification of iron chelation therapy.
Methods: We evaluated endocrine complications in 72 TM patients. At baseline, TM patients were treated with deferoxamine (DFO) alone. Thyroid and gonadal functions have been evaluated. Bone system was also investigated. Patients were randomly treated with DFO and deferiprone (DFP) (group A) or continued monotherapy with DFO (group B) or deferasirox (DFX) (group C) for 3 years. They were re-evaluated from an endocrinological and metabolic point of view. Iron metabolism was also re-assessed.
Results: 72 patients were followed over a period of 10 years. The frequency of iron overload complications at baseline were as follows: hypogonadism (n=24,33.3%), hypoparathyroidism (n=10,13.5%), diabetes mellitus (n=4,5.5%), hypothyroidism (n=19,26.3%), bile lithiasis (n=12,16.6%), kidney stones (n=8,11.1%) and osteoporosis (n=33,45.8%). In group A, there was a statistically significant reduction of the total body iron load, as indicated by ferritin levels. An improvement of endocrine status was demonstrated. Kidney and bile stones were also reduced whereas osteoporosis did not presented a significant regression. Furthermore, we found differences between group B and C according to incidence and prevalence of endocrinopathies.
Conclusions: Intensification of chelation with combined therapy and the achievement of normal ferritin levels, led to an amelioration of endocrine system. Since the origin of bone disease in TM is multifactorial and some of the underlying pathogenic mechanisms are still unclear, further research in this field is needed.

P2-d2-1026 Pituitary and Neuroendocrinology 4

Response of medical treatment in female paediatric and adolescents prolactinomas

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Introduction: Our aim is to analyze response to dopamine analogues in paediatric and adolescent female prolactinomas.
Methods: 32 girls and adolescent (mean age=18) harbouring prolactinomas (Mean prolactin= 512.97ng/ml (106-6000), mean tumour height=12.71mm (4- 50mm) are retrospectively analyzed under dopamine agonists (bromocriptine=30, cabergoline n=2), bromocriptine mean dose= 14.76mg/day (5-57mg), mean duration= 13 months (7- 36).
Results: The tolerance was good in 30 cases = 93.75%. Pubertal development was achieved in 27.27%, galactorrhea disappeared in 48% and normalization of gonadal function observed in 31.25%. Prolactin was normalized in 50%. Tumour reduction (30-100%) was observed in 78.57% and visual troubles disappeared in all cases.
Conclusion: In this study the tumoricide action was good, but anti prolactin action was mediocre probably because of imperfect compliance or fear to give high dose bromocriptine as cabergoline is not available in our country.

P2-d2-1027 Pituitary and Neuroendocrinology 4

Thyrotropinoma in an 11-year-old boy with type 1 autoimmune polyglandular syndrome (APS1)

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Introduction: Thyrotropinomas are rare pituitary adenomas, particularly in childhood.
Case study: 8-yrs old boy presented in 2002 hypoparathyroidism, and primary adrenal insufficiency. Mutation in locus R257X of AIRE-gen was revealed, confirming the diagnosis of APS-1. There were no signs of other endocrinopathies, including normal values of thyroid hormones. Elevated TSH 16.8 mIU/L (N 0.4-4), fT3 27.9 pM/L (N 2.5-5.8) and fT4 45.8 pM/L (N 11.5-23) were revealed in 11 yrs during routine follow-up. MRI showed endosuprasellar isointense mass size 26x32 mm with compression of optic chiasm. Ophthalmology examination detected bitemporal hemianopsia with normal visual acuty. The tumor was partially resected transsphenoidally. The pathologic specimen showed adenoma cells immunopositive for TSH, GH, SSTR5 and negative for LH, FSH, prolactin, ACTH, SSTR2. 5 days after surgery TSH, free T3 and free T4 dropped to normal, but 3 months after surgery TSH and thyroid hormones were still elevated. MRI showed significant residual tumor. Local radiation therapy (Total dose 55.8 Gy) was performed. The patient developed GH deficiency 1 year after irradiation. 3.5 years after irradiation (at age 15.3 years) the patient became euthyroid, and GH therapy (Rastan, JSC «Pharmstandard» manufactured, Russia) was started (his growth was 139.5, SDS -3.3). At 16.5 yrs the patient was started on sex steroids due to central hypohonadism. 7 yrs after irradiation the patient became hypothyroid,

and L-thyroxin was administred. Follow-up MRI scans showed significant decrease of tumor mass after irradiation.
Conclusion: This is the first case of coexistence of this 2 rare endocrine diseases in one patient.

P2-d2-1028 Pituitary and Neuroendocrinology 4

GH- and prolactin-producing pituitary adenoma with low somatostatin receptor 2 expression in a 16-year-old girl 15 years after heart transplantation

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Introduction: Pituitary tumours in childhood and adolescence occur with a reported prevalence of up to 1 per million children. Whereas craniopharyngiomas comprise the majority (80 to 90%) of pituitary neoplasms of children, hormone-secreting adenomas are extremely rare.
Case study: We report a 16-year old girl presenting with galactorrhoea for six months and progressive headaches. In view of a mildly elevated prolactin level of 896 mU/l (NR 89-827) a prolactinoma was suspected. MRI revealed a 1.6 cm sellar lesion with compression of the pituitary stalk and lifting of the optic chiasm. In addition GH was markedly elevated (73.8 ng/ml, NR < 8) as well as IGF-I and IGFBP3 concentrations. Oral glucose tolerance test failed to suppress GH indicating a mixed prolactin- and GH-producing adenoma. The patient was treated with long-acting octreotide for three months before transsphenoidal surgery without any effect on GH levels. Three days postoperatively, GH levels decreased to 1.02 ng/ml but one month later rose again to 3-4 ng/ml, however with normalization of IGF-I levels. Histopathology confirmed a GH- and prolactin-producing adenoma with an increased proliferation rate of 3 % and a low somatostatin receptor 2 expression (10-15 %). The patient's history is notable for a heart transplant at age one year after heart failure in neonatal enterovirus-associated dilated cardiomyopathy. At present the patient is still on immunosuppressive therapy. We judge the patient as being in partial remission but did not start any further medical or radiation treatment yet.
Conclusion: Acromegaly is associated with significantly increased morbidity and mortality. The morbidity risk in our rare patient might be increased considering the complicated medical history. Somatostatin analogues will probably be ineffective in view of low somatostatin receptors expression. The current follow-up comprises 3-monthly controls of GH and, IGF-I levels and cranial MRI.

P2-d2-1029 Pituitary and Neuroendocrinology 4

Etiologies of central diabetes insipidus in children

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Background: Central diabetes insipidus is a heterogeneous disease mainly due to lesions of hypothalamic nuclei or pituitary stalk caused by tumors of the suprasellar region or infiltrative diseases such Langerhans cells histiocytosis or sarcoidosis.
Objective and hypotheses: The aim of our study was to analyze the etiologies of central diabetes insipidus in children.
Methods: Medical records of 31 children (mean age of 7 years) were reviewed.
Results: Craniopharyngioma was the main etiology found in 71%, in 3.2% diabetes insipidus was secondary to autoimmune hypophysitis, in 3.2% it appears after radiotherapy for a germinoma of the pineal region, finally, in 22.6% it was considered as idiopathic.
Conclusions: We concluded from our study that tumors of the suprasellar region in particular craniopharyngioma are the main cause of central diabetes insipidus in children.

P2-d2-1030 Pituitary and Neuroendocrinology 4

Wolfram syndrome in twelve patients from a mountainous area where consanguineous unions are not unusual: phenotypical expression

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Background: Wolfram first reported the combination of juvenile-onset diabetes mellitus (DM) and optic atrophy (OA) in 1938. With the discovery of two other essential components, diabetes insipidus (DI) and deafness (D), Wolfram syndrome (WS) is now also known by the acronym DIDMOAD. Other, less common, manifestations include renal tract abnormalities, neuropsychiatric disorders and hypogonadism.
Objective: Aim of the present study was to evaluate WS phenotypical expression in a mountainous area of North-eastern Sicily, where consanguineous unions are not very unusual.
Population and methods: We evaluate the clinical findings in a study population of 12 WS Caucasian patients from 7 couples and 5 unrelated families of North-eastern Sicily area. They are aged between 9 and 29 years (mean age 22.1 ± 5.6 years). In order to definitely confirm that the 12 patients included in the present study are the only WS individuals aged under 30 who are currently living in Messina district, we have contacted all the other Units of our region.
Results: In all cases, DM was the earliest detected abnormality and its presentation occurred during the first decade with a medium age at diagnosis of 5.33 ± 3.11 years; conversely, diabetes insipidus and deafness occurred in a later period (mean age 14.9 ± 4.5 and 13.4 ± 6.8 years, respectively). Our series presented other less common clinical features, including psychiatric disorders, renal out-flow tract abnormalities, primary gonadal atrophy, and even bilateral cataract. In two patients, belonging to the same pedigree, we also observed two different congenital heart defects, one of which had been previously described in only one WS patient .
Conclusions:
a) In our series, diabetes mellitus onset was before 10 yrs in 11/12 patients and ten cases have already developed all four peculiar manifestations of WS by 26 yrs;
b) the finding of a cardiac malformation in WS children might not be quite fortuitous.

P2-d2-1031 Pituitary and Neuroendocrinology 4

Pitfalls in the diagnosis of GHD in children with hypothalamic and pituitary abnormalities

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Background: Diagnosing GH deficiency (GHD) in children often is a challenge. GHD is recognized through an appropriate clinical history and by demonstrating a reduced GH peak in accordance with normative values. It can be associated to hypothalamic-pituitary abnormalities.
Methods: We describe three children aged less than 6 years with decreased growth rate who were first evaluated for a medical history, physical examination and laboratory tests. They underwent classical stimulation tests (arginine and clonidine), arginine plus GHRH test (Arg+GHRH) and then MRI to study the hypothalamic and pituitary region. Serum IGF-1 and IGFBP3 were measured and bone age was determined according to Greulich and Pyle method in all subjects.
Results: All children showed a reduced GH response to the classical tests but a normal GH peak to Arg+GHRH. No other pituitary hormones deficiencies were recognized. The MRI showed pituitary hypoplasia in two children and pituitary hypoplasia with ectopic posterior pituitary in the third patient.
Conclusions: Our results appear to be noteworthy as our very young children -differently from adults- showed no correlations among the GH response to Arg+GHRH and to other clinical tests, or the IGF1/IGFBP3, or the MRI and

the clinical parameters.
Ghigo reported that the Arg+GHRH may fail to recognize GHD in children with partial impairment of pituitary stalk and Keller found no different GH response to Arg+GHRH in children with abnormal and normal MRI. Maghnie speculated that "this is probably due to a residual functional link between hypothalamic GHRH activity and somatotroph cells allowing some GH synthesis and release".
The aim of our report is to remind that the diagnosis of GH secretory dysfunction in very young children should be based not only on the GH response to the provocative tests, in particular Arg+GHRH, but also on the clinical signs and MRI findings.

P2-d2-1032 Pituitary and Neuroendocrinology 4

Congenital hypopituitarism and early onset of ACTH deficiency in a boy with 301-302delAG/150delA mutation of PROP1

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Background: PROP1 mutations are one of the most common causes of congenital combined pituitary hormone deficiency (CPHD). The 301-302 delAG and the 150 delA as well are already described as "hot spot" mutations.
Objective and hypotheses: Characterization of the phenotype in a boy with 301-302 del AG/150 delA from the Bulgarian pituitary transcriptional factor screening study.
Case study: Male, born after 1st, uneventful pregnancy, normal delivery, BW 3450g (50 centile), BL 52 cm (75 centile), TH-SDS 1.04; prolonged jaundice, micropenis, hypospadia, cryptorchidism neonatally. Growth delay noticed at 6 months by the mother. Diagnosis "isolated" GH deficiency (GHD) at 1y11m: short stature SDS^{h} -2.6, frontal bossing, nasal bridge depression, delayed bone age (BA) corresponding to 10-11m, BA/CA 0.4, severe GHD (GH peak after insulin < 3 ng/ml); rhGH start at 2 yrs. Central hypothyroidism diagnosed at 8y2m (TSH 0.9 mU/l, fT4 4.9 pmol/l with subsequent start of L-Thyroxin), followed by central hypocorticism diagnosed at 11y4m (nausea, vomiting, headache, low 24 hour urine and serum cortisol, introduction of hydrocortisone during stress) and hypogonadotropic hypogonadism (no spontaneous puberty, induction performed). Severe anterior hypoplasia of the pituitary by MRI. Strong candidate for PROP1 mutational screening performed in two steps: Bcg1 restriction - heterozygous for 301-302 del AG; direct sequencing - compound heterozygous for 301-302 delAG/150 delA. Follow up: final heght 183 cm (SDS_h 1.0), need for lifelong hormonal substitution, transferred to a specialized endocrine and reproductive center for adults after 18 yrs.
Conclusions: The patient represents an unique opportunity for studying the phenotype compared to other patients with the same genotype. Characteristic features::early, "isolated" GHD, consecutive manifestation of all tropic deficiencies, panhypopituitarism at 12 yrs, severe hypoplasia of the adenohypophysis.
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P2-d2-1033 Pituitary and Neuroendocrinology 4

Adolescent girl with McCune Albright syndrome combined with pituitary gigantism; treatment with lanreotide and cabergoline

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Introduction: Lanreotide and cabergoline therapy has shown promising results in acromegalic patients. However, experience in pediatric patients is limited. We describe the clinical course of a 12yr old girl with McCune Albright Syndrome (MAS) and pituitary gigantism.
Case study: At 2yr she presents vaginal bleeding, ovarian cysts, fluctuating thelarche and cafe au lait spots. The diagnosis of MAS was made with(+) mutation of Protein G(Arg201Cys) in blood. At 4yr due to persistent rhinorrhea, we performed a sinus CT and bone scintigraphy, which evidenced craniofacial polyostotic fibrous dysplasia with sphenoid, ethmoid, frontal bone, left maxillary sinus/malar bone, and right parietal/occipital bone involvement. Later she had osteolytic activity in the right scapula and humerus, supra-acetabular region and both femurs. At 7yr she had a height 2.76SD, indicating an increase in growth velocity. Brain MRI revealed a pituitary macroadenoma of 2cm with suprasellar extension. Laboratory: IGF-1=790ng/ml, GH suppression test GH=55.5ng/ml at 120 minutes and prolactin 658ng/ml. Her parents decide to suspend controls. The patient returns at 11yr(bone age 10.6yr) with a height of 162cm(2.6SD), acromegalic features, completed puberty, and a history of right femur/humerus fractures at 6yr and 10yr. Laboratory: central hypothyroidism, elevated IGF-1 and prolactin. Surgical extirpation of macroadenoma was not possible due to the extensive cranial involvement. Treatment was initiated with levothyroxine, cabergoline and lanreotide(60mg/month). Currently the patient is euthyroid with normal prolactin and near normal range IGF-1 after 3 doses.
Conclusion: We report an adolescent girl with MAS associated with gigantism due to a pituitary macroadenoma. Since a partial response was obtained, the dose of lanreotide will be increased to 90mg/month and evolution will be assessed. An effective treatment for GH hypersecretion remains a problem, especially in pediatric patients with MAS.

P2-d1-1034 Programming/Epigenetics 2

Birth-weight is associated with insulin resistance, dyslipidaemia and hypertension in children, adolescents and young adults with type 1 diabetes mellitus

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Background: Restricted fetal growth is associated with an increased risk for insulin resistance, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease in adulthood. Currently there is no epidemiologic data available on the association of birthweight with insulin resistance in children, adolescents, and young adults with type 1 diabetes mellitus (T1DM).
Objective: To investigate the association of birthweight with insulin resistance, duration of remission, and metabolic control in subjects with T1DM.
Population and methods: Cross-sectional analysis of a subgroup of 7861 subjects (age range 2.5 - 25 ys) identified from the DPV database system diagnosed with T1DM for more than two years who were born either small- (SGA, birthweight < 10th perc., n=1046), normal- (NGA, birthweight 10th-

90th perc., n=5958), or large-for-gestational age (LGA, >90th perc., n=857).
Results: Mean age in the study population was 15.1 ± 3.8 ys. Age, age at diabetes diagnosis, diabetes duration, duration of diabetes remission, and mean A1c did not differ between birthweight categories. Adjusted for potential confounders (age, sex, diabetes duration, treating diabetes center, treatment regimen, and BMI z-score), SGA subjects had a significantly higher insulin requirement (0.96 IE/kg) than NGA (0.91 IE/kg), and LGA subjects (0.88 IE/kg, p< 0.01). SGA subjects were significantly more often affected by dyslipidemia (39.9% vs. 33.1% (NGA) vs. 29.2% (LGA), p< 0.001) and hypertension (29.0% vs. 24.5% (NGA) vs. 20.9% (LGA), p< 0.01) than subjects with normal or high birthweight.
Conclusions: Low birthweight is a predictor for higher insulin requirements as a surrogate marker for insulin resistance in young patients with T1DM. Furthermore, patients with T1DM born small-for-gestational age are at higher risk for dyslipidemia and hypertension independent of potential confounders.

P2-d1-1035 Programming/Epigenetics 2

Serum biochemical markers related to insulin sensitivity in children born from pre-eclamptic pregnancies

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Background: Preeclampsia occurs in 5-7% of all pregnancies. Previously, preeclampsia has been associated with later insulin resistance and cardiovascular morbidity in affected subjects. Additionally, it has been shown that blood pressure is increased in children born from preeclamptic pregnancies.
Objective and hypotheses: The aim of our study was to determine whether maternal preeclampsia influences insulin sensitivity (IS) or metabolic markers associated with it in the offspring during childhood.
Subjects and methods: We studied sixty 12-year-old children born from preeclamptic pregnancies (PRE) and 60 age- and sex-matched control subjects born from non-preeclamptic pregnancies (non-PRE). IS was estimated by Quantitative Insulin Sensitivity Check Index (QUICKI), and serum concentrations of high molecular weight (HMW) adiponectin, leptin, IGFBP-1, osteocalcin, fibroblast growth factor 21 (FGF-21), and triglycerides were measured.
Results: The means of fasting blood glucose, serum insulin, QUICKI, HMW-adiponectin, leptin, triglycerides, IGFBP-1, osteocalcin or FGF-21 did not differ between the PRE and non-PRE groups (P>0.05 for all). The PRE children with low IS (the lowest QUICKI tertile, n=20) had significantly higher mean serum leptin (20.1 vs 12.2 ug/l, P=0.007) and triglycerides (1.02 vs. 0.85 mmol/l, P=0.008), and lower mean IGFBP-1 (49.9 vs. 75.0 ug/l, P=0.007) and osteocalcin (90 vs. 148 ug/l, P< 0.001) when compared to the PRE children with better IS (n=40). The means of BMI did not differ between these two subgroups (19.0 vs. 18.9, P=0.433). In BMI-adjusted multiple logistic regression analysis of the whole study population (n=120), low IGFBP-1 (P=0.008), osteocalcin (P=0.006), FGF-21 (P=0.019) and high triglycerides (P=0.019) associated with low IS.
Conclusions: The PRE children did not have reduced IS compared with non-PRE children. In the PRE children, low IS associated with higher serum leptin and triglycerides, and lower IGFBP-1 and osteocalcin levels.

P2-d1-1036 Programming/Epigenetics 2

Clinical characterization and molecular classification of fifteen Korean patients with pseudohypoparathyroidism type Ia, Ib, Ic and pseudopseudohypoparathyroidism

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Background: Pseudohypoparathyroidism (PHP) is defined as resistance to the action of parathyroid hormone. PHP and pseudopseudohypoparathyroidism.
(PPHP) are rare disorders resulting from genetic and epigenetic aberrations in the *GNAS* locus.
Objective and hypotheses: Clinical characteristics and molecular analysis in PHP and PPHP were investigated.
Methods: A total of 15 patients with (P)PHP from 13 unrelated families [5 with PHP Ia, 6 with PHP Ib, 1 with PHP Ic, and 3 with PPHP] were characterized clinically and molecularly. Clinical features included presenting symptoms, AHO features, and resistance of hormones such as PTH, TSH, GnRH, and GHRH. Direct sequencing and methlyation-specific miltiplex ligation-dependent probe amplification (MS-MLPA) of *GNAS* were performed. Deletion in *STX16* was confirmed by long PCR. In order to exclude paternal disomy, microsatellite marker analysis was performed on patients who showed only a paternal methylation pattern and the parents of PHP Ib patients if parents' DNA is available.
Results: Five patients with PHP Ia and 3 patients with PPHP harbored different heterozygous 6 mutations in *GNAS*. Six patients with PHP Ib showed loss of the maternal-specific methylation pattern. One patient with PHP Ib had 3-kb microdeletion in *STX16*. Four patients whose parents' DNA were available did not show paternal disomy. One patient with PHP Ic revealed no abnormalities in direct sequencing, MS-MPLA, and RT-PCR of *GNAS*. In addition, the patient with PHP Ic showed normal activity of G s alpha protein and no abnormalities in chromosomal microarray.
Conclusions: Molecular analysis is warranted for exact diagnosis because patients suspected PHP may experience life-threatening hypocalcemic episode. *GNAS* mutation analysis and MS-MLPA are useful methods for confirming the diagnosis of (P)PHP. Further studies need to identify the responsible gene for PHP Ic.

P2-d1-1037 Programming/Epigenetics 2

Review of the clinical scoring systems in Silver-Russell Syndrome and development of modified diagnostic criteria to guide molecular genetic testing

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Background: About a half of all children with a clinical diagnosis of Silver-Russell Syndrome (SRS) have a detectable molecular genetic abnormality (maternal uniparental disomy of chromosome 7 or hypomethylation of *H19*). The selection of children for molecular genetic testing can be difficult for non-specialists because of the broad phenotypic spectrum of SRS and the tendency of the facial features to mitigate during late childhood. Several clinical scoring systems for SRS have been developed by specialist researchers but the utility of these for guiding molecular genetic testing in routine clinical practice has not been established.
Objective and hypotheses: To evaluate the utility of four published clinical scoring systems for genetic testing in a cohort of patients referred to a clinical service laboratory.
Methods: Individuals with suspected SRS referred for molecular genetic testing of H19 methylation status or mUPD7 were scored according to published

criteria. Anthropometric measures and clinical features were requested from the referring clinician using a custom-designed questionnaire.
Results: 36 of 139 (25.9%) patients referred for testing had a genetic abnormality identified. Comparison of four published clinical scoring systems demonstrated that all included subjective criteria that could be difficult for the general clinician to assess. We developed a novel, simplified, scoring system utilising four objective, easily measured parameters (low birthweight, postnatal growth faliure, relative macrocephaly and asymmetry) that performed similarly to the most sensitive and specific published scoring system.
Conclusions: Effective utilisation of genetic testing by clinicians without specialist clinical genetics training will be facilitated by the development of targeted testing protocols are based on robust objective clinical features and that are designed for use in a busy clinical practice rather than a research setting.

P2-d1-1038 Programming/Epigenetics 2

Long-term effects of cow milk feeding in infancy on metabolic health

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Background: The results of a survey conducted in Nizhny Novgorod, Russia in 2001 had revealed a low prevalence of exclusive breastfeeding and high incidence of whole cow's milk feeding in infants.
Objective and hypotheses: To evaluate consequences of whole cow's milk feeding in infancy on Body-Mass Index (BMI), blood pressure (BP) and insulin metabolism. We hypothesize that such feeding practice has long-term negative effect on metabolic health.
Methods: Case-control cohort analysis of 79 children, aged 6 years (74.95±17.8 months), recruited from a clinical population (n=436) who had participated during infancy in the 2001 feeding practice survey. Participants were divided into 2 groups according to type of feeding in infancy: those breastfed for a minimum of 9 months.
(BF; n=36), and those who had a high daily volume of cow's milk during the first year (CM; n=43). We measured BMI, BP, fasting and 2-hour glucose and insulin levels following an oral glucose load (1.75 g/kg; 75g max).
Results: There was a clear trend separating BMI between the groups, beginning at 6 months and persisting through the most recent measurement (6 years) at which time the difference had become 1.3 times higher (β=1.697, p=.003). CM children showed higher systolic and diastolic BP (99.58 vs 93.39 mm Hg, p< 0.001; 68.23 vs 63.67 mm Hg, p=0.003), and a marginally significant upward trend in 2-hour insulin (18.5 vs 9.52 mcIU, p=0.049). There was no significant difference in glucose level between the groups either in fasting or 2-hour levels. There was a significant correlation between BMI, BP and insulin level (p=0.001-0.006).
Conclusions: These findings suggest that dietary patterns in infancy have immediate effects into toddlerhood and through age 6 years. Cow's milk feeding in infancy may predispose children to increased body mass, BP and insulin resistance.

P2-d1-1039 Programming/Epigenetics 2

Prader-Willi syndrome: influence of the genotype on the mental performances

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Background: Prader-Willi Syndrome (PWS) is a rare neurodevelopmental disorder caused by paternal micro-deletion (p-DEL), maternal uniparental disomy (m-UPD) or imprinting defect of paternally inherited genes in the 15q11.2-q13 region. Mental retardation appears to be due to p-DEL.
Objective: To examine differences in p-DEL (DELs) versus m-UPD (UDPs) PWS patients in intellectual and behavioral functioning.
Methods: Nine PWS children (6-16 years), six DELs and three UDPs, were evaluated. The protocol required an in-depth psychological assessment:
1) Interviews with childrens' parents,
2) Intellective assessment (WISC III)
3) Behavioral examination
(*CBCL, K-SADS-PL, VINELAND ADAPTIVE BEHAVIOR SCALES, ABC-Aberrant Behavior Checklist-community*).
Results: (mean ± standard deviation) WISC-III total quotient was 47.3 ± 8.9 in DELs and 66.7 ± 10.7 in UPDs. UPDs had higher verbal (51.2 ± 8.0 versus 67.7 ± 9.0) and performance
(54.8±8.4 versus 74.7±9.3) IQ scores than DELs. Verbal IQ was lower than IQ performance in both groups. DELs showed: 50% minor mental retardation range, 33% moderate retardation (IQ 35 - 49), 16.7% major retardation (IQ < 35). UPDs showed: 66.7% minor mental retardation, 33.3% borderline intellective functioning (IQ 70-89), close to inferior normal limit. WISC III profile was different: in verbal area, both groups fell into specific subtest (arithmetic reasoning, memory of numbers); while in the performance, DELs showed a strength in subtest reconstruction of objects, which expresses visual-perceptual ability. UPDs fell in these subtests areas: cipher and search for symbols that reflect a diminished graph-motor ability.
The behavioral evaluation tests showed that DELs had more maladaptive behaviors and psychiatric symptoms than UPDs, especially for aggressive and compulsive (skin-picking), fits of anger and hyperactivity.
Conclusion: DELs PWS patients seem to have a more severe phenotype and a greater cognitive impairment, than UPDs ones.

P2-d1-1040 Puberty and Gonads 4

A new variant in the human luteinizing hormone receptor (hLHR) causing Leydig cell hypoplasia: functional characterization

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Background: The hLHR mediates, in the testis, the effect of LH on Testosterone (Te) biosynthesis. Inactivating mutation of the hLHR in male cause hypergonadotropic hypogonadism (HH) due to the gonadal resistance to the LH action.
Case report: Here we report the case of an adolescent that come to the pediatricians at the age of 13 years old for micropenis and cryptorchidism. Hormone evaluation showed LH=10.9 IU/L; FSH=6.5 IU/L; Te total=< 0.69nM/L with a conserved response to GnRH test (LH net increase=60.4; FSH net increase=3.86) and a slight increase of Testosterone to hCG stimulation (Te pre=< 0.69 nM; post=1.49nM). A second evaluation at the age of 15 years old showed LH=40.8 IU/L; FSH=16.0 IU/L; Te total= 4.09 nM/L. No other hormone deficit were present. Testis biopsy showed Leydig cell absence and germinal line elements were not observed.
Method: The sequence analysis of the hLHR gene showed the presence of a compound heterozygosity, being one variation, c.1847C>A p.S616Y, already described in association to HH, and the other, c.29 C>T p.L10P, a new identified variant. We then decide to characterized the p.L10P new variant by in vitro experiments. We subcloned this variant in a plasmid vector and we tested its ability to stimulate cAMP accumulation in COS-7 transfected cells by performing concentration-effect curves.
Results: The results showed a reduced Emax and an equal EC_{50} in comparison with the wild-type hLHR. We then tested its expression level at the plasma membrane by two different methods. The FACS analysis confirmed a marked reduction of the p.L10P variant with only a partial recovery of the expression after cell permeabilization. The western blotting analysis was also confirming the reduced amount of the variant protein.
Conclusions: Our in vitro results demonstrate the pathogenic role of the p.L10P variant, which is to be considered a novel loss-of-function mutation significantly contributing to the Leydig cell hypoplasia of this patient.

P2-d1-1041 Puberty and Gonads 4

Hyperandrogenaemia is associated with insulin resistance independently of adiposity in young polycystic ovary syndrome patients

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Background: Hyperandrogenemia is one of the most important characteristic of polycystic ovary syndrome (PCOS) patients. The relationship between androgens levels, insulin resistance and adiposity is still intensively debated in adult PCOS and is even more unclear in adolescents with PCOS.
Objective and hypotheses: Therefore the aim of our study was to analyse whether there is a link between circulating androgens and insulin resistance in adolescents with PCOS.
Methods: Subjects were 95 post-menarchal adolescent with PCOS mean age 18,38±1,5 yrs, range 13-20 yrs, mean BMI 25,5±6,6 kg/m2, range 15-45 kg/m2, retrospectively selected from our PCOS database. The diagnosis of PCOS was established in the presence of clinical and/or paraclinical hyperandrogenism in association with menstrual irregularity. Anthropometric indices of adiposity (body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR)), total testosterone (TT), fasting blood glucose and insulin, sex hormone binding globulin (SHBG) were reviewed. HOMA-IR was calculated as index of insulin resistance and free androgen index (FAI) as a marker of hyperandrogenemia. SPSS version 17 was used for statistical analysis. Data with non-gaussian distribution were log-transformed before analysis.
Results: We found that HOMA-IR was positively correlated with FAI ($p< 0,0001$), BMI ($p< 0,0001$), WC ($p< 0,0001$) and WHR ($p< 0,0001$), but not TT. We constructed few models of multivariate liniar regression with HOMA-IR as dependent variable and FAI and markers of adiposity as independent predictors and we found that, after adjusting for adiposity FAI was independently associated with IR revealed by HOMA-IR.
Conclusions: In conclusion, in our population of young PCOS adolescents hyperandrogenemia is related to insulin resistance independent of all adiposity markers, reflecting the early involvement of androgens in PCOS pathogenesis.

P2-d1-1042 Puberty and Gonads 4

Lack of functional compensatory activity of the seminiferous tubules remaining testis in monorchid boys

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Background: Monorchia is the existence of only one testis, which usually undergoes compensatory hypertrophy. It is not clear if it can also compensate the function of the absent one.
Objective: To investigate testicular function in monorchid boys.
Methods: In a retrospective semi-longitudinal study, we compared serum AMH, testosterone, FSH and LH between 89 monorchid patients, ages 1.1-18.7 yr, and 421 normal boys.
Results: In monorchid boys, AMH was significantly reduced, except in 11-12.9 yr (Table). FSH was significantly elevated in patients > 13 yr. LH was significantly elevated in groups 11-12.9 yr and >15 yr. Testosterone was significantly reduced only in patients 9-12.9 yr.
Similar results were observed when the analysis was performed according to Tanner stages. In a subgroup of 20 monorchid patients in whom a history compatible with gonadal damage of the remaining testis could be ruled out, AMH was significantly reduced as compared to age-matched controls in all groups except the 11-12.9 yr and >15 yr. Testicular volume correlated significantly with AMH in boys 3-9 yr.
Conclusions: The correlation between testicular volume and AMH indicates that at least in part Sertoli cell is responsible of compensatory hypertrophy. However, functional compensatory activity is not complete, as suggested by AMH reduction and FSH increase.
Furthermore, results in patients with no history compatible with gonadal damage of the remaining testis rule out that reduced AMH is related to the concomitant dysfunction of the remaining testis.

	Serum AMH (pmol/Liter) Monorchids	Serum AMH (pmol/Liter) Controls	
	Median (Interquartile range)	Median (Interquartile range)	p
6 m-2.9 yr	324 (221-820)	920 (708-1240)	0.0026
3-8.9 yr	403 (203-637)	596 (420-873)	0.0005
9-10.9 yr	330 (196-446)	685 (402-905)	<0.0001
11-12.9 yr	165 (62-281)	257 (71-536)	0.1339
13-14.9 yr	48 (30-67)	72 (51-120)	<0.0001
>15 yr	37 (20-44)	73 (51-113)	<0.0001

[Serum AMH in Monorchids boys compared to Controls]

P2-d1-1043 Puberty and Gonads 4

Correlation between total testosterone and free testosterone with anti-Mullerian hormone and clinical features of hyperandrogaenism in adolescent girls

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Background: Absence of mutual relation between hyperandrogenemia and androgen excess (AE) symptoms stays one of the biggest challenges in understanding hyperandrogenism (HA). AMH is becoming more essential in assessment of follicular development block which is another most important component of HA. Data on application of these parameters in adolescents is limited.
Objective and hypotheses: To assess correlation between TT and its free calculated fraction with clinical features of HA and AMH.
Methods: Adolescent girls with clinical hyperandrogenism (2 of 3 symptoms present- hyperandrogenemia, oligomenorrhea, hirsutism). All patients were 2 years past menarche. Pelvic transabdominal ultrasound was performed before the 7th day of menstrual cycle and hirsutism was assessed by F-Gallway scale. Total testosterone (TT) and sex-hormone binding protein (SHBP) were measured by chemiluminescence method on the 3-7th days of menstrual cycle. Free testosterone (FreeT) was calculated by using free ISAAM application. AMH was measured by ELISA, DSL. All the analyses were held in the same laboratory. Reference range for TT was 0.7-2.7 nmol/l, for FreeT 0.004-0.034 nmol/l, there were no references for AMH.
Results:

	Total testosterone (TT), n=65, 1.89±0.92 nmol/l	Free Testosterone (FreeT), n=59, 0.04±0.02
Hirsutism	0.06, p>0.05	0.32, p<0.1
Number of menstrual cycles per year	-0.17, p>0.05	-0.18, p>0.05
Volume of ovaries	0.22 p>0.05	0.16, p>0.05
Antu-Mullerian hormone (AMH), ng/ml n=47	0.14, p>0.05	0.04, p>0.05

[Hormonal and clinical features of AE]

Level of TT was elevated in 15,4% of girls (10/65), FreeT was elevated in 41% (23/56). We have also investigated interconnection between AMH and hirsutism, number of menstrual cycles per year and volume of ovaries and found no significant correlations between those parameters ($p< 0.05$ for all).
Conclusions: AMH a known marker of follicular arrest was independent of TT and FreeT in our study. Absence of correlation between TT, FreeT and clinical presentation of HA is present in adolescents and corresponds to data in adult population.

P2-d1-1044 Puberty and Gonads 4

Relationship between fetal weight and maternal nutritional status, serum concentrations of insulin, leptin and adiponectin during normal gestation

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Background: Fetal growth depends on adequate oxygen and nutrition and several growth and genetic factors. These are important early in gestation whereas the maternal environment attains more importance later.
Objective and hypotheses: Access the relationship between birth weight and maternal nutritional status expressed as body mass index (BMI), and insulin, adiponectin and leptin serum concentrations.
Methods: Twenty-five women aged 13 to 34 years (median: 22) were followed for a gestation. At each quarter BMI was determined and blood samples for hormone measurements were obtained. At birth, estimated gestational age was calculated as well as fetal weight, length, Apgar score and the newborn was classified into small for gestational age (SGA), appropriate (AGA) or large (LGA). Maternal hormonal tests were processed through automated systems (Cobas 6000/411-Roche-Hitashi). Insulin concentrations were determined by electrochemiluminescence (Roche-Diagnostics kits), adiponectin (Abcam Inc.Cambridge,MA,USA) and leptin (Millipore Corporation, St. Charles,Missouri,USA) were determined by enzyme immunoassay (ELISA). Correlations between hormonal concentrations and fetal weight employed Pearson' test.
Results: Twenty-five infants (12 boys, 13 girls) with a gestational age of 39 weeks ±1.75 born without complications; 19(76%) were AGA, 3 (12%) were SGA, and 3 (12%) were LGA. Fetal weight (3.0±0.58kg) showed significant and positive correlations with BMI determined before pregnancy and in the first, second and third quarter but did not correlate with quarterly concentrations of insulin (20.2 ± 22.7, 11.2 ± 7.0, 18.6 ± 14.6 µIU/mL), adiponectin (1781.1 ± 83.8, 1777.3 ± 85.0, 1791.3 ± 89 pg/mL) or leptin (16.3 ± 10.3, 17.7 ± 14.2; 18.2 ± 10.6 ng/mL).
Conclusions: Maternal nutritional status, which is multifactorial, has more importance in determining the fetal weight than isolated concentrations of insulin, leptin and adiponectin.

P2-d1-1045 Puberty and Gonads 4

Testicular functions in regularly blood-transfused thalassemia major patients

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Background: Regular blood transfusion and iron chelating therapy have improved quality of life and increased longevity in Thalassemia patients, but blood transfusion also increases the frequency of endocrine complications due to iron overload. Hypogonadism is the most common complication caused by iron deposition in pituitary gland or gonads or both.
Objective: To evaluate the testicular function in patients with Thalassemia major who have been received regular blood transfusion by Tanner assessment and measuring serum levels of LH (Luteinizing hormone), FSH (Follicle stimulating hormone), testosterone and AMH (anti-Müllerian hormone).
Study design: Cross sectional study.
Population: Patients with Thalassemia major aged between 8-18 years who have had regular blood transfusion were enrolled. The control group consisted of 64 healthy boys with age- and genital Tanner-matched.
Result: Twenty-eight patients with Thalassemia major aged 11.7 ± 1.8 (8-14.9) yrs, were included in the study (11 in prepuberty, 17 in puberty and no delayed puberty). The trend of AMH level on age in Thalassemia major patients and normal control were similar, but the levels were higher in Thalassemia group particularly in Tanner II (459.1 vs 113.17 pmol/L, $p< 0.01$). The testosterone levels were lower in Thalassemia group compared to normal control particularly in Tanner II (4.6 vs 46.1 ng/dL, $p< 0.01$). Serum level of FSH and LH was not significantly different between Thalassemia and control group in all Tanner. The AMH level had negative correlation with age of maximum ferritin level and the testosterone level had positive correlation with the age of start chelation therapy.
Conclusion: There is no delayed puberty in Thalassemic patients who were received regular blood transfusion. Leydig cell function, but Sertoli cell function, is subnormal in Thalassemia major patients who have been received regular blood transfusion even though they had normal age of pubertal onset.

P2-d1-1046 Puberty and Gonads 4

Should patients with Down syndrome be screened for testicular microlithiasis?

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Background: Testicular Microlithiasis (TM) is a rare condition characterized by asymptomatic calcification of seminiferous tubules and is considered as a precursor of testicular germ cell tumors. The prevalence of TM has been reported higher in patients with Down's syndrome (DS) than general population.
Objective: To determine the prevalence of TM in our patients with DS.
Subjects and methods: Male patients with DS confirmed by chromosomal analysis and followed regularly in medical genetics and pediatric endocrinology clinics of a tertiary hospital were prospectively evaluated using high resonance ultrasound. For every patient with DS an age match healthy non-DS volunteer was recruited and the results were compared.
Results: Fifty testes from 25 patients aged between newborn to 19.3 years and 50 testes from 25 age matched non-DS controls were studied. While nine patients with DS (36%) had TM, none of controls had TM. Mean testicular volumes of patients with DS did not differ significantly from the control group. Cryptorchidism was found in 5 patients with DS (3 unilateral, 2 bilateral) and in 2 controls (1 unilateral, 1 bilateral). In DS group; patients with TM were significantly older than patients without TM [mean age (min-max) was 8.44 (2.0-19.3) years and 2.39 (0.1-12.1) years, respectively, $p=0.002$]. TM was found positively correlated with age ($r=0.568$, $p=0.003$). Of nine patients with TM, only one had cryptorchidism, thus TM was found not related to cryptorchidism. All nine patients with DS and TM had normal serum baseline levels of alpha-fetoprotein and beta-human chorionic gonadotropin. Those patients will be further assessed for development of testicular germ cell tumors.
Conclusion: Based on the high prevalence found in our study, we suggest that male patients with DS should be screened for TM in childhood.

P2-d1-1047 Puberty and Gonads 4

Primary ovarian insufficiency in an adolescent exposed to in-utero chemotherapy

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Introduction: Primary ovarian insufficiency (POI) is a heterogeneous disorder characterized by amenorrhea, hypoestrogenism and hypergonadotropism. Causes include chromosome disorders, autoimmune conditions, genetic mutations, environmental insults and idiopathic etiology. The associated infertility is distressing to adolescents.
Case study: A Caucasian adolescent female presented with secondary amenorrhea following normal growth, pubertal development, menarche and regular menses. She was delivered at 34 weeks gestation following chemotherapy during the last two trimesters for mother's cardiac leiomyosarcoma. There was no family history of infertility. Both parents had café au lait spots. She had no dysmorphism; no thyromegaly; multiple café au lait spots; no intertriginous freckling or palpable neurofibromas; neurologically intact; no Lisch nodules; Tanner stage 5. Karyotype was 46,XX; anti-ovarian, 21-hydroxylase, and celiac antibodies normal; ACTH and adrenal steroids normal; TSH 1.02 mIU/L, anti-Müllerian hormone (AMH) undetectable, LH 41 mIU/mL, FSH 70 mIU/mL, and estradiol 3.7 pg/mL. Pelvic ultrasound showed endometrial atrophy with normal uterine and ovarian volumes. She was referred to reproductive

endocrinology to determine if any oocytes could be retrieved (unlikely due to undetectable AMH) and to discuss potential assisted reproductive technologies. Estrogen replacement therapy and counseling were initiated.
Conclusion: Her POI was most likely iatrogenic. Diagnostic criteria for neurofibromatosis type 1 were not met. Although fetal effects of chemotherapy are generally less after the first trimester, the reproductive system is not completely developed. Leiomyosarcoma is an aggressive soft tissue sarcoma treated with alkylating agents which can cause gonadal failure. It is plausible that similar effects could affect the developing reproductive system. Due to a paucity of information on long-term chemotherapy effects on the fetus, more research is necessary.

P2-d1-1048 Puberty and Gonads 4

High prevalence of polycystic ovarian syndrome in adolescents with type 1 diabetes mellitus: is there a difference according to NIH and Rotterdam criteria?

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Background: Polycystic Ovarian Syndrome (PCOS) is more frequently described in Type 1 Diabetes Mellitus (T1DM) women than in non-diabetic women. In adolescent with T1DM, this prevalence and associated factors are not published.
Aim: To evaluate the prevalence and phenotype of PCOS in T1DM adolescent and to determine the features associated with this disorder.
Patients and methods: 53 included adolescents with T1DM (11.9 to 18.8 years old) and a gynecological age more than 2 years (2 to 5 years) were categorized in 2 groups (with and without PCOS) according to Rotterdam and NIH criteria.
Results: 23/53 (43.4%) and 14/53 (26.4%) adolescents had PCOS according to Rotterdam and NIH criteria, respectively. 19/53 (35.8%) adolescents had Polycystic Ovarian Morphology (POM). Family history of Type 2 Diabetes Mellitus (T2DM) was significantly more frequent in PCOS-Rotterdam and PCOS-NIH patients than non PCOS adolescent (52.4% vs 20%, p=0.01 and 66.7% vs 23.1%, p=0.005 respectively). PCOS adolescents had younger gynaecological age (according to Rotterdam criteria) and older thelarche age (according to NIH criteria) than non PCOS (2,3 vs 2,8 years, p=0,03; 11,6 vs 10,5 years, p=0,02, respectively). Adolescents with PCOS according to NIH criteria had a tendency for an older age at diabetes diagnosis than non PCOS adolescents (10.8 vs 8.2 years, p=0.052). HbA1c was negatively correlated to ovarian volume (Rho=-0,46, p=0,01) and annual mean dose of insulin was positively correlated to Free Androgen Index (Rho=0,5, p=0,03).
Conclusion: Adolescents with T1DM had a high prevalence of PCOS. Our results suggest that an age of diagnosis of T1DM close to puberty would be a risk factor of PCOS. Improved metabolic control is associated with an increased ovarian volume. However, we found no difference in HbA1c between PCOS and non PCOS according to Rotterdam criteria. Thus, we question the relevance of morphological ovarian criteria in the diagnosis of PCOS in T1DM adolescents.

P2-d1-1049 Puberty and Gonads 4

Prospective study of ovarian function secondary to fetal ovarian cyst

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Background: Neonatal management of ovarian cyst is controversial and few studies describe ovarian outcome.
Objective and hypotheses: The main objectif is to know the rate of ovarian recuperation after the occurrence of a fetal ovarian cyst. Ovarian function was evaluated by the presence or absence of US ovarian follicle and hormonal status.
Methods: 89 ovarian cysts were detected at the 3rd trimester of gestation. These cysts were fluid or simple appearance in 46 cases, bleeding with heterogeneous appearance in 40 cases, bilateral in 3 patients.Parents were advised that emergency surgery was possible at any time (painful abdominal syndrome or ultrasound changes).Their written consent was obtained. The programming of the monitoring according to a predetermined schedule during the first year of life combined a medical and surgical consulting, ovarian ultrasound, tumor markers and hormonal dosage.
Results: At birth 40 cysts were heterogeneous, 49 were fluid. It has not been detected organic tumors. In all cases , tumor markers were within normal values . During 1st of life, coelioscopy with ovariectomy was performed in 5 cases due to recent ovarian torsion, and punctures of cysts was necessary because of the large volume: US guided punctures in 5 cases,surgical in 4 cases.

Aspect of cyst	No follicles N=29	Ovary with follicles N=60	Total N=89
Heterogenous cyst	N=28	N=12	N = 40 P< 0.0001
Fluid cyst	N=1	N=48	N=49 P< 0.0001
AMH (ng/ml)	1.5 ± 1.1 n=16	4.1 ± 3.1 n=34	P= 0.0024

[Results]

There is no difference in size between fluids and heterogeneous cysts and no difference in hormonal levels except for AMH levels. Cystic regression of fluid cysts is constant (98% functional ovary), it was in 60 days , dependent on the initial size, Only 30% of heterogeneous cysts have functional ovary.
Conclusions: The risk benefit balance is not in favor of neonatal systematic surgery. We emphasize the need for multidisciplinary care and close monitoring in neonatal period.

P2-d1-1050 Puberty and Gonads 4

Clinical follow-up of ovarian cysts in childhood and adolescence: a multicenter study

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Background: Ovarian cysts are uncommon during childhood, but their prevalence is increasing as a result of advancements in diagnostic technologies.
Objective and hypotheses: To investigate the findings of childhood ovarian cysts at the time of their admission and during follow up and to evaluate treatment options.
Methods: A total of 64 patient files in 9 pediatric endocrinology clinics with a diagnosis of an ovarian cyst (>10mm) were retrospectively investigated. Size and localization of the cyst, age, symptoms at presentation, treatment modalities and problems during follow up were recorded.
Results: The average diameter of cysts detected antenatally (n=14) was 55.7±27.1mm and all were simple cysts. None of them exhibited torsion. Seven patients underwent oophorectomy, 3underwent cystectomy, 4cysts regressed spontaneously. One patient developed CPP during follow up. Mean age of the patients diagnosed postnatally (n=50) was 8.4±5.0 years. The average diameter of the cysts was 41.4±24.1mm.
Presenting symptoms were abdominal pain(n=11), breast enlargement (n=10), vaginal bleeding (n=9), menstrual irregularity(n=5) and hirsutism (n=2). In 13 asymptomatic patients, ovarian cysts were detected incidentally. Although most of the cysts were simple cysts(n=45), 2 patients had granulosa cell tumors, 2 had teratomas and 1had a dermoid cyst. Five patients had ovarian torsion. However torsion occurred mostly in patients with large cyst(>40mm), it was detected in 1patient with a small cyst(< 20mm). Eleven patients underwent oophorectomy, 5 underwent cystectomy and spontaneous regression was observed in 26 patients. Pharmacological treatment was used in 12 patients alone or as an addition to surgical therapy. CPP developed in 3patients during follow up.
Conclusions: Most of the cysts presenting during childhood have a favorable prognosis. However there may be coexisting problems or complications such as tumors, torsion and CPP; hence these patients should be followed up with close monitoring.

P2-d1-1051 Puberty and Gonads 4

Phenotypic and cytogenetic findings in girls with "Y" sequences in their karyotypes

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Introduction: The presence of Y chromosome material in females is associated with the risk of development of gonadal tumors having an increased age related risk.
Aim: To evaluate retrospectively the clinical, phenotype and cytogenetic characterization of patients presenting "Y material in their karyotypes who were subsequently gonadectomized.
Patients and methods: Twenty six patients treated at the Division of Endocrinology and Surgery were admitted at 0.5 through18 years of age. Cytogenetic studies were performed in peripheral blood cultures with conventional banding G and high resolution techniques. Current cytogenetic analyzes were performed with FISH to asses molecular sequences of "Y" chromosomes. Gonadectomy was performed through laparoscopy.
Results: Patients were evaluated at a mean age of 9.8 ± 5.5 years of age. Sixteen girls were first evaluated because short stature, one because a palpable tumor, 5 for arrested puberty and/or amenorrhea and 2 edemas of hands and feet. 21/26 had typical Turner Syndrome stigmata. Only 3 patients had very few signs of virilization: 2 mild clitoris hypertrophy and one lower posterior fusion labia. Mean height at diagnosis was -2.4 ± 1.6 SDS. Karyotypes were: 46, XY (n = 4), 45, X/46, XY (n = 11), 45, X/46, X + mar (n= 2), 45, X but with SRY gene sequences, DYZ3 (Y centromere) and DYZ1 (Y heterochromatin) positive (n = 2), in the remaining patients, karyotypes showed different complex mosaics. All patients were gonadectomized without complications. In 8 of them gonadal tumors were found (30.6%): 4 gonadoblastomas, 3 had gonadoblastoma and dysgerminoma, and 1 had an undifferentiated gonadal tumor. Ages of these patients ranged from 4.4 to 18.
Conclusions: The presence of gonadal tumors in children with "Y" chromosome and / or "Y" hidden sequences highlights the importance of performing early gonadectomies and genetic diagnoses in girls with short stature.

P2-d2-1052 Puberty and Gonads 5

Hypogonadotropic hypogonadism and the gene for fibroblast growth factor receptor 1 - successful pregnancy through gonadotropin therapy and intracytoplasmic sperm injection

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Background: Gonadotropin therapy (GT) is frequently used to induce fertility in patients with hypogonadotropic hypogonadism (HH). We previously reported that GT is effective in conferring fertility in Kallmann syndrome's patient with *FGFR1* mutation.
Objective: To study the effects and the consequences of combination of GT and assisted reproductive techniques in HH caused by heterozygous FGFR1 mutations.
Clinical report: One Japanese family was examined. The 43-year-old father had a history of delayed puberty and cleft lip and palate. The 42-year-old mother experienced menarche at the age of 11, but has been having anovulatory cycle. They were seen at a local hospital because of infertility. The father was diagnosed with HH and received GT with hMG (150 IU i.m. twice per week) and hCG (5000 IU i.m. twice per week). Subsequently, sperm concentration increased to 60 x10^6 count/mL. The mother was diagnosed with anovulatory menstruation and received intermittent ovulation induction as treatment for fertility. Successful fertilization was induced through combination of both regular ovulation induction and intracytoplasmic sperm injection (ICSI) after GT of father, but implantation did not occur. After ten years of GT with father, combined with ovulation induction of the mother as well as ICSI, there was successful conception and a baby boy was finally born. The son however, was born with a micropenis and cryptorchidism suggestive of HH and cleft lip and palate.
Molecular studies: Genetic screenings were performed (*KAL1*, *FGFR1*, *PROK2*, *PROKR2*, *NELF*, *TAC3*, *TACR3*, and *GNRH1*). Heterozygous *FGFR1* Q285X mutations were identified in both the father and son.
Conclusions: Fertilization treatment using a combination of GT and ICSI is useful to achieve pregnancy between a father with HH and a mother having a history of anovulatory cycle, but with a risk of transmitting the mutation and the disease phenotype to the next generation suggestive of father's HH and cleft lip and palate.

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Girls with McCune Albright syndrome: is there a place for unilateral ovarian surgery during childhood?

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Background: Major issue during girls' McCune Albright syndrome (MAS) management is the repetition of precocious puberty episodes for which poorly efficient treatment are available.
Objective and hypotheses: To show feasibility and results of early unilateral ovarian surgery during their management.
Methods: In a referral centre for paediatric endocrinology and gynaecology, we reviewed the charts of all the patients managed for MAS from 1988 to 2012. We determined if there was a preferential side of ovarian cysts recurrence. We also focused on the evolution of two patients that were surgically managed very early in the intercourse of the disease as compared to others medically treated.
Results: 11 female patients with median current age of 19 years were included. Nine girls were medically managed with poor results: six always developed ipsilateral ovarian cysts. Only three developed bilateral ovarian cysts and two of them were also the most severe patients of the cohort.Medical treatments included Cyproterone acetate, Ketoconazole, Letrozole or Anastrozole.
Two other patients were rapidly operated and with a 13 and 7 years follow-up respectively, they are free of clinical recurrence.
Conclusions: Regarding the results of our series it seems predictable to early determine if patients will have a bilateral or a unilateral ovarian disease. Thus, considering the severe ovarian morbidity of MAS revealed in infancy and the quiet evolution of patients who underwent early ovarian surgery in our series, we suggest that early unilateral ovarian surgery could be discussed in the management of MAS paediatric patients.

P2-d2-1054 Puberty and Gonads 5

The management of prepubertal gynaecomastia in two monozygotic twins with Peutz Jeghers syndrome: from aromatase inhibitors to radical mastectomy

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Introduction: Prepubertal gynecomastia is characterized by the presence of palpable unilateral or bilateral breast tissue in boys, without other signs of sexual maturation. It may be the endocrine expression of rare syndromes, such as Peutz Jeghers syndrome (PJS). The purpose of this study is to evaluate the efficacy of anastrozole and to describe an innovative surgical approach.
Case study: We present the follow-up clinical history of two twins (eleven years old) with PJS, bilateral prepubertal gynecomastia and testicular multifocal calcifications, probably a large-cell calcifying Sertoli cell tumors (LSCT), responsible for estrogens excess, already described by us in a previously published report.
Both patients were treated with anastrozole for two years. Bone age advancement and gynecomastia diminished during anastrozole treatment.
Nevertheless therapy was discontinued for a sharp reduction in growth velocity (1,6 cm/year, < third percentile for age and sex). Consequently both twins showed relapse of gynecomastia, with abundant painful breasts tissue, corresponding a female Tanner stage B3. For this reason, after stopping medical treatment, both performed radical mastectomy by "modified" Webster technique.
This approach allows us to remove totally the gland, to avoid recurrence of gynecomastia with a good aesthetic results.
Conclusions: In this study,
1) we have shown the importance of a multidisciplinary approach to prepubertal gynecomastia due to the synergy of pediatricians, radiologists and plastic surgeons;
2) we observed the validity and feasibility of the "modified" Webster technique in terms of aesthetic and functional results, patient satisfaction and absence of complications in this rare case of gynecomasthia with persistent estrogen overproduction;
3) we reported a rare adverse effect of anastrozole, i.e. growth velocity decrease, which can limit its use in some clinical contexts.

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Various endocrine disorders in children with 45,XY,der(13;14)(q10;q10) karyotype

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Background: 45,XY,der(13;14)(q10;q10) karyotype can have problem of infertility associated with more or less severe oligospermia in male adult. In addition this karyotype carrys reproductive risks such as miscarriage or infertility in female adults. However, reports on phenotype of this karyotype in children is very rare.
Objective and hypotheses: This study was done to see various phenotypes of this karyotype in children.
Methods: Between Jan 2007 and Dec 2012, children whom were diagnosed as 45,XY,der(13;14)(q10;q10) karyotype by chromosome analysis were analyzed retrospectively.
Results: Eight children were diagnosed as 45,XY,der(13;14)(q10;q10) karyotype. They are 4 boys and 4 girls. Age ranges between 5yr 6 months and 12 yr 4 months. Phenotypes of study patients consisted of 1 hypogonadotrophic hypogonadism, 1 short stature, 2 normal short stature with delayed bone-age more than 2 years, 3 early puberty and 1 precocious puberty. As shown here, 45,XY,der(13;14)(q10;q10) karyotype shows wide range of phenotypes from infertility associated with hypogonadotrophic hypogonadism to precocious puberty. They also showed short stature with delayed bone-age.
Conclusions: It can be said that 45,XY,der(13;14)(q10;q10) karyotype shows various phenotypes from infertility to precocious puberty in children. Further large-scaled studies are necessary.

P2-d2-1056 Puberty and Gonads 5

Lower cortisol response after OGTT related to glucocorticoid sensitivity

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Background: The cortisol response to oral glucose load in PCOS and metabolic syndrome is not well understood. Decreased cortisol release after OGTT has been noted in obese subjects, which correlated with degree of insulin resistance and obesity. We believe that glucocorticoid (GC) sensitivity is associated with cortisol response in OGTT, as shown in comparison to in vitro GC binding assay.
Methods: We recruited 15 patients, 12 females with PCOS and 3 males with metabolic syndrome. GC sensitivity was evaluated by F-Dex binding assays. GC index (GCI) was calculated as area under curve (AUC) (Normal value 300 ±40, calculated from 12 control patients).
A lower GCI represents decreased level of GC sensitivity. A 2-hour OGTT was performed on same patients where serum cortisol levels were obtained at 30-minute intervals. Cortisol index (CI) was calculated as AUC.
Results: A positive correlation between GCI and CI was noted, indicating that lower GC sensitivity in a patient, the less of a cortisol response to OGTT and lower AUC ($R=0.77$, $p< 0.0001$).
Cortisol response was statistically different between GC sensitivity groups at 60, 90, and 120 minutes (Serum cortisol (mcg/dl): GC resistant patients at 60' 11 ± 4.5, 90' 7 ± 1.9, 120' 7 ± 1.6; GC Sensitive patients at 60' 21 ±10, 22 ± 12, 12 ± 6).

Conclusions: Low cortisol response during OGTT was associated with increased GC resistance. One suggested model can be cortisol metabolism regulation by 11β-HSD1 in hepatocytes and availability of Glucose-6phosphate intracellular.

P2-d2-1057 Puberty and Gonads 5

Clitoromegaly in a 3-year-old child: first presentation of a neurocutaneous syndrome?

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Background: Enlargement of the clitoris with or without signs of androgen excess suggests androgen production by either the ovaries or adrenal disorders. A rare cause is a neurocutaneous syndrome.
Objective and hypotheses: We present a case of a three years old girl with clitomegaly.
Methods: She was first seen at the age of three due to parents' concerns of an enlarged clitoris noted since birth that had grown in size over the last year. On examination she was clinically well, prepubertal, growing along the 75th percentile(Weight, Height), head circumference >97th percentile, development appropriate for age; clitoris was enlarged(4cmx1cm). Coarse facial features and >10 'café- au- lait spots maximum size 4.5cmx3cm were noted.
Results: Karyotype was 46,XX. Routine and endocrine investigations, bone age, and a short Synacthen test(table 1) were within normal limits; FSH 1.9mIu/ml(0.2-11), LH 0.1mIU/ml(0.1-0.5), oestradiol 37.3(22-99.1pmol/l); normal thyroid function. Both abdominal ultrasound and MRI showed normal adrenal glands and female internal genitalia with appropriate size for age. T2-weighted brain MRI showed hyperintense lesions compatible with neurofibromatosis type 1(NF1); MRI of genitalia revealed a hypertrophic clitoris with no lesions. The patient was referred to paediatric surgeons for further assessment.
Conclusions: NF1 is an autosomal progressive disorder with an incidence approximately 1:3000 live births.Features include cafe-au-lait spots, neurofibromas, hamartomas, macrocephaly, vascular lesions. Involvement of the external genitalia is extremely unusual. Clitoromegaly is a frequently seen congenital malformation, but acquired clitoral enlargement is rare. A detailed history and physical examination are required for the evaluation of clitoral enlargement because it may result from a variety of conditions.

Time (mins)	0	30	60
17OHP(ng/ml)	1.12	4.24	5.11
Cortisol(nmol/l)	550	9.62	1074

[Short Synacten Test]

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Clinical and molecular characterization of children with idiopathic hypogonadotropic hypogonadism

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Background: Idiopathic hypogonadotropic hypogonadism (IHH) is a clinically and genetically heterogeneous disorder. It was usually diagnosed when someone absent of pubertal development ≥17 years in females and ≥18 years in males. But there was no clear diagnostic criteria of IHH in children. To date, there is less data in children of IHH. Loss-of-function mutations in the genes encoding anosmin-1 (KAL1) have been described this syndrome.
Objective: To characterize the phenotype, karyotype, and molecular basis of children younger than 18 years old with idiopathic hypogonadotropic hypogonadism (IHH).
Methods: 17 children (include 16 aged from 10y2m to 17y boys and 1 thirteen years old girl) with IHH including 13 KS, without definite family history were studied. Review of medical data. A total of 9 KS patients were studied for KAL1 mutations. KAL-1 coding regions/splice junctions were subjected to polymerase chain reaction (PCR)-based DNA sequencing.
Results: The chief complain of 11/17 cases including a girl is no sexual signs and among them, 8/10 boys had small penis or/and cryptorchidism as well. Another six patients' complain is abnormal external-genitalia. 13 /17 boys had olfactory abnormalities and were diagnosed with KS. 11/17 patients have hypoplasia of the olfactory bulb or olfactory groove on the MRI. We got 9 KS blood sample and identified only one KAL1 mutation, a splicing mutation IVS7 + 1G>A.
Conclusions: High proportion of KS and small penis or cryptorchidism patients are seen in male children IHH than in adult. The olfactory bulb MRI is an important hint for KS diagnosis in children. we should pay more attention on DSD, for asking the sense of smell and do the MRI of olfactory bulb when necessary. That is concordance with report in adult that low positive rate is in KS in KAL gene mutation.

P2-d2-1059 Puberty and Gonads 5

Girls with central precocious puberty during 5 years after completion of long-term treatment with GnRH agonist

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Background: Gonadotropin-releasing hormone agonists (GnRHa) are very effective in suppression of pituitary-gonadal axis.
Objective: To evaluate development in girls after long-term therapy with GnRHa.
Methods: 34 girls with central precocious puberty (CPP) (n=21 idiopathic CPP; n=13 organic CPP), treated for 3.0 yrs (median; range 1.0-7.1) with D-Trp6-GnRH agonist (Decapeptyl depot 3.75 mg; Ferring® or Diphereline S. R. 3 mg; Ipsen® monthly) were followed-up. At the end of therapy, median age was 11.1 yrs (range 9.4-14.1). Standard GnRH test (LHmax/FSHmax) at the end, 3 mths, 1 and 2 yrs after therapy (until menarche), volume of ovaries and uterus at the end, 3 mths, 1, 2, 3, 4 and 5 yrs after therapy were assessed. Results were compared with previous time point. Menstrual cycle was analysed yearly.
Results: LHmax/FSHmax 0.3±0.3 (mean±SD) increased within 3 mths to 1.2±0.7 ($p< 0.001$) and to 3.0±3.2 ($p< 0.01$) 1 yr after therapy. Ovarian volume 2.2±0.9 ccm increased within 3 mths to 3.3±2.0 ccm ($p< 0.01$), in 1 yr to 4.4±1.7 ccm ($p< 0.05$) with no another change. Uterus volume 4.2±1.7 ccm increased within 3 mth to 9.8±5.0 ccm ($p< 0.05$), in 1 yr to 21.7±7.8 ccm ($p< 0.05$), 2 yrs to 37.0±17.6 ccm ($p=0.05$), with no change later. Menarche was reached at the age 12.7±1.2 yrs; 1.6±1.0 yrs after therapy, earlier in ICPP group (1.4±0.6 yrs vs. 1.9±1.4 yrs in OCPP) ($p< 0.01$). Disturbances of menstrual cycle were found in 10% ICPP and 54% OCPP girls 5 yrs after therapy.
Conclusions: Suppression of pituitary-gonadal axis after long-term depot GnRHa therapy in girls with CPP was fully reversible. Volume of uterus and ovaries corresponds with rapid increase of gonadotropin levels within first year after therapy. During post treatment period, development of uterus corresponds with the biological age. Compared with general population, incidence of irregular menses did not differ in ICPP group. In OCPP girls, disturbances of menstrual cycle are in close relationship to their diagnosis.

P2-d2-1060 Puberty and Gonads 5

The cut-off point of sex hormone in simply identifying central precocious puberty and isolated premature thelarche in girls

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Background: There is overlap in the test value of basal sex hormone and peak of LH and LH/FSH after GnRH stimulation test between idiopathic central precocious puberty (ICPP) and isolated premature thelarche (IPT). It affects diagnosis.
Objective and hypotheses: To explore the cut-off point of basal sex hormone, peak of LH and LH/FSH after GnRH stimulation test between identify-

ing ICPP) and IPT in girls.
Methods: 217 girls because of early breast development were enrolled. The serum levels of basal estradiol and LH, peak LH and LH/FSH after GnRH stimulation test were detected and analysed retrospectively. According to the diagnosis criteria of ICPP and follow up, they were divided 2 groups, ICPP group (n=109) and IPT group(n=108). The two groups were compared and the cut-off points were determined accordingly.
Results: The estradiol, basal LH, peak LH and LH/FSH levels of the ICPP group were significantly higher than that of the IPT group. The areas under the ROC curve(AUC) were peak LH/FSH> peak LH> basal LH> estradiol. The cut-off point of the peak LH/FSH was 0.59, the sensitivity and specificity were 98.17% and 99.07%. And the cut-off points of peak and basal LH, estradiol were 5.07mIU/ml, 0.24mIU/ml, 31.78pg/ml respectively. Combing the cut-off points of the peak LH/FSH and LH, the sensitivity and specificity of this diagnosis criteria were 98.17% and 100%.
Conclusions: The cut-off points of peak LH/FSH 0.59 and peak LH 5.07mIU/ml have higher sensitivity and specificity in differential diagnosis between ICPP and IPT simply.

P2-d2-1061 Puberty and Gonads 5

Body mass index (BMI) evaluation in girls with idiopathic central precocious puberty (ICPP) during and after treatment with GnRH analogs (GnRHa)

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Introduction: GnRH analogs have been used in treatment of ICPP for several decades. Their effectiveness on adult height improvement has been widely studied. However, their impact on BMI is still controversial.
Objective: To assess BMI in ICPP girls during treatment with GnRHa and when reaching adult height.
Methods: A retrospective study of 117 ICPP girls, treated for a minimum of 2 years was performed (mean age at diagnosis: 7.6, range 2.7-9.2 years). BMI-SDS at basal, 1 and 2 years of GnRHa treatment was analyzed. In addition, 60 girls were also evaluated when adult height was reached. Patients were categorized according to BMI at the start of therapy into 3 groups:
normal weight (NW, n=56),
overweight (OW, n=43) and
obese (OB, n=18).
Changes in BMI-SDS were analyzed by ANOVA for repeated measurements.
Results: Basal SDS BMI (mean ±SD) was: in the NW group 0.29±0.7, in the OW group 1.54±0.2 and in the OB group 2.41±0.3. NW girls significantly increased BMI between basal and 1 year, mean: 0.42 SDS ($p < 0.001$). There were no differences in BMI between 1 and 2 years of treatment. OW girls showed a significant BMI increase (mean 0.2 SDS) at 1 year ($p < 0.05$) without differences between 1 and 2 years of treatment. In the OB group there was no difference in BMI along treatment. Girls who had achieved adult height showed a significant decrease in BMI compared with the start of GnRHa (mean difference 0.56 SD -$p < 0.001$) and compared to BMI at 1 year of treatment (mean difference 0.75, ($p < 0.001$).
Conclusion: Moderate increment in BMI was observed at 1 year of GnRHa treatment which persisted at 2 years of treatment in normal and overweight ICPP girls. However, no further increment in BMI was observed in already obese girls. Although changes observed on BMI throughout the first years of GnRHa treatment do occur, this does not lead to further obesity since a significant improvement on BMI is observed when these girls achieve adult height.

P2-d2-1062 Puberty and Gonads 5

Age at menarche in girls with coeliac disease

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Background: Several studies have shown that celiac disease can impair women's reproductive life eliciting delayed puberty.
Objective and hypotheses: The aim of this study was to evaluate the age at menarche in coeliac disease CD patients and their sisters'.
Method: This study covers a population menarcheal adolescents with CD listed in the Department of Pediatrics "C" CHU Oran, Algeria. Controls were represented by their sisters healthy living witnesses in the same house. All patients and sisters were asked for information on the age at menarche. olso we analyzed the correlation between age at menarche and socio-economic level to search the factors that influencing the age at menarche.
Results: 174 CD patients and 174 sisters healthy controls were compared in a case-control study. The mean age at diagnosis was 3.6 ± 5 years. The current mean age was 24.71 ± 5.19 years. The mean follow-up was 20 ± 4.5 years. The mean age at the time of the investigation sisters controls was 26.76 ± 7, 22. The mean age at menarche in CD girls (n = 174) was 14.56 ± 1.63 years, and in their sisters (n = 174), 13.74 ± 1.36 years ($t = 6.9$, $p < 0.0001$). In addition, a significant positive correlation between age at menarche and socio-economic level has been found ($p = 0.02$).
Conclusions: The age at menarche in patients with CD was significantly increased to age at menarche in sister's. Significant positive correlation between age menarche and socio-economic level has been found.These findings support the hypothesis that the age at menarche in CD girls is regulated by gluten-free diet and other genetic and environmental factors.

P2-d2-1063 Puberty and Gonads 5

Increased leptin levels in girls with premature thelarche

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Background: It has been reported that there is a relationship between circulating leptin and sex steroid hormones and leptin is able to stimulate estrogen secretion by increasing aromatase activity in adipose stromal cells and breast tissue. Leptin receptors have been also shown in mammary epithelial cells and it has been suggested that leptin is involved in the control of the proliferation of both normal and malignant breast cells.
Objective and hypotheses: The aim of this study was to investigate circulating leptin levels in girls with premature thelarche (PT).
Methods: In this cross-sectional study; we comprised 26 girls (mean aged 7.1 ± 0.8) referred for evaluation because of the appearance of breast buds before the age of 8 years and judged clinically to have PT, as well as 21 healthy age-matched prepubertal girls who served as controls. Breasts were assessed by visual inspection and palpation using the rating scales of Tanner and Marshall.
Results: The mean ages and BMI SDS of the study and control group were not different ($p > 0.05$). There was no significant difference for hormonal parameters including FSH, LH and estradiol between girls with PT and the control subjects ($p > 0.05$). The serum leptin levels were found significantly higher in the study group compared with the healthy controls (2.7 ± 2.4 *vs.* 1.1 ± 1.1 ng/mL, p: 0.007) despite their similar age and BMI-SDS.
Conclusions: Our study demonstrated that serum leptin levels were consistently higher in girls with PT than in healthy children. The role of circulating leptin in PT is probably related to increase in directly growth stimulating effect of leptin on mammary epithelial cells or increase in sensitivity of breast epithelial cells to estrogen with inducing functional activation of estrogen receptors by leptin in breast tissue.

P2-d3-1064 Puberty and Gonads 6

Idiopathic central precocious puberty is more prevalent than it is believed to be in boys

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Background: Central precocious puberty (CPP) is known to be rare in boys and is underlied by organic pathologies such as tumors. There's an increased tendency towards earlier puberty in populations, and some reports involve males.
Objective and hypotheses: As timing of puberty gets earlier, it can be projected that number of boys with idiopathic CPP can increase. The aim of this study is to analyze etiology of CPP in boys, and to differentiate the characteristics of idiopathic vs organic causes.
Methods: 75 boys with CPP diagnosed in the last ten years are included. The chronological, height, bone ages, BMI and height SDSs, pubertal stage, hypophyseal MRI are evaluated. Basal and stimulated gonadotropin and testosteron levels are used in the diagnosis.
Results: Mean chronological age at diagnosis was 8.0±1,6 years (9 month-9.6 years). 35.9% of the patients were at Tanner stage 2, the remaining at either stage 3 or 4. 53/75 (70.7%) of the patients with no underlying pathology on MRI were diagnosed as idiopathic CPP. 17 of the remaining 22 had space occupying lesions i.e. arachnoid cyst, hamartoma, adenoma, glioma and craniopharyngioma and 5/22 had developmental anomalies of the central nervous system. Four patients diagnosed as idiopathic CPP had attention deficit hyperactivity disorder. The only significant difference between idiopathic and organic groups was age of presentation (mean age 8.3±1.3 and 6.7±1.6 years respectively, p:0.003).
Conclusions: The prevalence of organic pathology associated with CPP, is reported up to 90% in boys. In the current study organic pathology was shown in only one third of male patients with CPP. This may be related to a new trend towards earlier age in timing of puberty in boys.

P2-d3-1065 Puberty and Gonads 6

Pelvic ultrasonography in the diagnosis of isolated premature thelarche

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Background: Isolated premature thelarche is defined as a benign condition in patients aged below 8 years, usually without progression to precocious puberty and bone age acceleration. Ultrasonography is a noninvasive imaging method for assessing disorders in children.
Objective and hypotheses: To compare pelvic ultrasound appearance with hormonal activity of the pituitary-gonadal axis in girls with isolated premature thelarche (IPT).
Methods: 102 girls with IPT (Tanner stage 2-3), mean age 2±1.4 years (0.04 -7 years), mean weight 12.3±4.3 kg, mean height 85.0±13.6 cm (45±31 percentile), mean BMI 16.4±1.7 (46.38±27.5 percentile).
The concentration of inhibin B, oestradiol, FSH, LH, prolactine, TSH, FT4, lipids and liver enzymes were estimated. Inhibin B was measured by ELISA (DSL, USA), the other hormones by LIA (DPC, USA).
Pelvic ultrasound examination was performed by one gynaecologist.
Results: Thyroid hormones levels were within normal ranges in all of the patients. Oestradiol concentration was below estimation threshold in 88% of them. Mean inhibin B level was 6.3±10.6 pg/ml, LH 0.15±0.07 IU/l, FSH 4.2±2.7 IU/l, prolactine 15,1±12 ng/ml.
The patients were divided to two groups: group 1 (40%) - nonhomogenous ovarian structure with visible follicles on ultrasound examination (paucicystic, multicystic) and group 2 (60%) with homogenous ovaries.
No significant differences of the levels of measured hormones were observed in both groups of patients.
Conclusions: Pelvic ultrasonography cannot be used instead of hormonal assessment in patient with IPT. Early stage of development of follicles does not depend on FSH, and is not connected with secretion of inhibin B.

P2-d3-1066 Puberty and Gonads 6

Profiles of pubertal markers in relation to clinical pubertal development in representative cohorts of healthy lean and obese children

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Rationale: We aimed to investigate dynamics in puberty and fertility markers in relation to pubertal development in children and adolescents. Considering that obesity may be accompanied by precipitated pubertal development, we compared sex steroid profiles between lean and obese children.
Methods: The cohort included 3000 children and adolescents aged 1.3 to 20.0 years with 2332 children from a representative Caucasian pediatric population and 668 obese children. After exclusion of syndromes, contraceptional medication, and precocious/retarded pubertal development, we determined estradiol, progesterone, testosterone, LH, FSH, DHEAS, SHBG, albumin and prolactin by immunoassay in the remaining 2915 probands.
Results: In our representative normal cohort, we saw an expected highly significant correlation of all hormonal markers with age and pubertal stage. DHEAS was very similar between boys and girls. Besides sex specific differences in estradiol and testosterone, progesterone was very similar in absolute levels and slope during entire pubertal development in boys and girls. Boys had lower FSH levels at the beginning of puberty, but catched up with girls at pubertal stage 4. For LH we observed the most distinct increase with pubertal onset in boys and girls. Prolactin increased with puberty particularly in girls, while SHBG decreased with age more pronouncedly in boys.
Compared to lean children, DHEAS, and progesterone were pronouncedly lower in obese children, while SHBG, testosterone and in girls estradiol were higher. SHBG and albumin showed strongest correlations with BMI SDS in girls ($r=-0.62$, $P< 0.001$) and boys ($r=-0.54$, $P< 0.001$), and hence differences in free testosterone index were most evident between lean and obese children.
Conclusion: We describe age and gender specific dynamic for major puberty and fertility markers of normal, healthy children and adolescents across all pubertal stages. Obesity is accompanied by deranged peripheral sex steroid profiles.

P2-d3-1067 Puberty and Gonads 6

Precocious puberty and gynaecomastia in a boy affected by a contiguous gene syndrome caused by a chromosome 19p deletion including STK11

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Background: Peutz-Jeghers syndrome (PJS) is a rare, autosomal dominantly inherited disorder, caused by germline mutations in the STK11 tumour suppressor gene (19p13.3), which explains the increased risk of GI and extra-GI malignancies such as breast cancer and gynaecological carcinomas. The phenotypic spectrum of PJS also includes frequent occurrence of tumours considered to be benign or of low malignant potential such as Sertoli tumours of the testis and certain sex cords tumours of the ovary. Only few descriptions on patients with STK11 deletions involving the neighbouring genes exist.
Objective: To describe a boy with intellectual disability, partial idiopathic epilepsy, gonadotropin-independent precocious puberty with gynecomastia, and STK11 deletion.
Methods: Clinical examination, testicular ultrasound (US), biochemical measurements and karyotype analyses.
Results: A 9-year-old boy presented with bilaterally enlarged testes (7 ml),

pubarche (P2), and gynecomastia (B3, confirmed with US). He did not have café-au-lait spots. Testicular US showed few microcalcifications (biopsy is now scheduled). TSH and prolactin levels were normal. Testosterone, estradiol and the results of GnRH stimulation test were prepubertal. Plasma AMH level was high (>220 ng/ml) and inhibin B level was normal for the child age. Karyotype was normal, but the microarray analysis showed a de novo partial deletion of chromosome 19p13.3 (1.104.885-1.384.778) including the STK11 gene. Subsequently, the child was noted to have hyperpigmented macules in the lips and their vermillion border and oral mucosa, findings typical for PJS. GI-examinations are currently on-going.
Conclusions: In this boy, the phenotypic features including precocious puberty, gynecomastia, pigmentation of the lips, intellectual disabilities and partial idiopathic epilepsy, are consistent with a contiguous gene syndrome associated with a deletion of chromosome 19p13.3 region encompassing 10 genes including STK11.

P2-d3-1068 Puberty and Gonads 6

Physiological estrogen replacement therapy with transdermal patches in girls with hypogonadism: a clinical observational study

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Background: The pubertal estrogen replacement therapy (ERT) consist of two parts, low estrogen doses to promote pubertal growth, to and to initiate development of secondary sexual characteristics and a second part with "high" estrogen doses for development and finish secondary sexual characteristics and growth/bone development.
Objective and hypotheses: In the present study we have studied how use of nocturnal administrated transdermal estrogen patches (Evorel®) works in an out-patient setting, by assessing the reported dose in relation to achieved morning level of serum estradiol . Focus on doses that results in similar morning levels of estradiol as in gonadarche 7-24 pmol/L.
Methods: The study material consisted of serum samples sent for estradiol determination to the GP-GRC laboratory, at the Queen Silvia Children's Hospital, Göteborg, as part of ERT. Estradiol concentrations were determined with diethyl ether extraction step prior to RIA (Spectria® Estradiol RIA, Orion Diagnostica) with detection limit of 4 pmol/L. Exclusion criteria pubertas tarda, pubertal arrest. Serum estradiol concentrations were analysed in relation to given dose Evorel® (estradiol µg/kg).
Results: The samples were submitted from 18 clinics from all over Sweden. 93 observations on 58 individuals were included in the study. 23 had diagnos Turner syndrome. There was a linear relationship between serum estradiol and given dose, $r=0.56$, $r^2=0.31$, $p< 0.0001$ for all observations and $r=0.65$, $r^2=0.40$, $p< 0.0001$ for observations in Turner syndrome (n=42).
Conclusions: For initiation of ERT/pubertal induction with nocturnal administrated Evorel® matrix patch, the recommended doses are 0.05-0.07 µg/kg, equivalent to 2-4 µg of Evorel® patch with the goal of similar morning levels of estradiol as in gonadarche 7-24 pmol/L. In older girls when breast development is a higher priority, we recommend to start with doses of 0.08-0.12 µg/kg, corresponding to 3-6 µg of an Evorel® patch.

P2-d3-1069 Puberty and Gonads 6

The effect of extremely adverse critical life events in childhood on age at menarche in a developing country

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Background: The age at menarche is controlled by genetic and environmental cues, including nutrition, socioeconomic status and critical psychosocial life events. We assessed girls who had been through extreme war conditions and malnutrition in northern Uganda from 1996-2006.
Hypotheses: The age at menarche is determined by
1. Current nutritional, social background.
2. Adverse critical life events in childhood.
Method: This was a comparative cross sectional study of both rural and urban secondary school girls in post conflict northern Uganda. At a mean (±SD) age of 8.7±3.1 years, 151/274 were displaced into camps, where malnutrition was common. Structured questionnaires were administered to 274 girls aged 16.9±1.6 years to determine their age at menarche in relation to nutritional status, and adverse critical life events in childhood. Age at menarche was defined in years and nutritional status was defined by BMI.
Results: The mean (±SD) age at menarche was 13.5±1.4 years, with urban and rural secondary school girls' ages at 13.4+1.5 and 13.6±1.3 years, respectively (NS). The mean (±SD) BMI was 21.7±2.6 & 21.4±2.1, in urban and rural girls respectively (NS). Age at menarche positively correlated with paternal education ($p =0.033$, $r = 0.122$) but did not correlate with current BMI (except for the hip circumference which correlated negatively with menarche age ($r =-0.128$, $p=0.035$), childhood critical life events such as abduction, displacement into camps, loss of first degree relatives (212/274), or the gender of siblings in the household during the war.
Conclusion: Adolescent girls of northern Uganda, showed resilience to extreme hardship during childhood in terms of their menarcheal age. Critical life events, school location, and current BMI did not affect age at menarche. Lower social class (by lack of paternal education) was associated with later menarche. Thus, recent environmental cues have stronger influence on puberty than childhood events do.

P2-d3-1070 Puberty and Gonads 6

Testosterone therapy in males with Duchenne muscular dystrophy

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Background: Glucocorticoid (GC) therapy slows disease progression in Duchenne Muscular Dystrophy (DMD), but causes severe endocrine adverse effects, including delayed/absent puberty and osteoporosis. Pubertal delay exacerbates osteoporosis and affects quality of life (QOL), but is typically ignored in DMD care. Furthermore, osteoporosis treatment options are limited in DMD. Testosterone (T) is used to treat constitutional delay and hypogonadism in young males, and osteoporosis in elderly males.
Objectives: To determine if T therapy 1) improves bone mineral content (BMC), 2) increases lean body mass (LBM) and 3) results in hypothalamic-pituitary-gonadal (HPG) activation in DMD.
Methods: Retrospective review of T therapy in adolescent GC-treated DMD males with delayed puberty. Primary outcome was change in BMC at 1y on T therapy. Secondary outcomes included measures of body composition and HPG activation.

Results: 26 males were treated with T for 3.0±1.0y; 17 met inclusion criteria for BMC analysis. Subjects were aged 14.9±1.3y, most non-ambulatory. Boys were treated with GC (for 8.0±2.1y prior to T), calcium/vitamin D, and 11 with bisphosphonates. BMC was low at T start, even if adjusted for height: whole body BMC Z-score (BMCZ) was -6.0±1.7, height-adjusted (BMCZ-Ht) -3.5±1.6; lumbar spine (LS) BMCZ was -3.9±1.2, LS BMCZ-Ht -1.4±0.9. LS BMC did not change prior to T, but increased by 2.5±0.9g (mean±SEM, $p< 0.05$) at 1y on T. LS BMCZ declined prior to T (by -0.5±0.1, $p< 0.05$), but stabilized during the first year on T, even after adjusting for height. LBM did not change significantly pre-T, but increased by 1.7±0.6kg at 1y on T ($p< 0.05$). 11/24 (46%) boys who were pre-pubertal at T start developed HPG activation on T.
Conclusions: T therapy may benefit spine BMC and increase muscle mass in DMD. T may trigger HPG axis activation in some cases. Further study is needed to assess T effects on bone health, muscle strength, pubertal outcomes and QOL in DMD.

P2-d3-1071 Puberty and Gonads 6

Serum INSL3 concentrations increase during male puberty in the Mongolian population of East Asia

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Background: Insulin-like factor 3 (INSL3) has become a promising new candidate for classification of male puberty stages since it is secreted by the Leydig cells of the testis and increases with the elevated Tanner stages.
Objective: To investigate serum INSL3 levels in individuals with normal puberty in Mongolian population of East Asia.
Population and methods: Fasting blood samples were taken from 80 individuals to assess serum INSL3 concentrations. 75 male students with different Tanner stages (14, 14, 15, 17, and 16 from Tanner 1 to Tanner 5 stage, respectively) were included in this research and 5 female students as control. Serum INSL3 concentrations were determined by an enzyme immunoassay (EIA) kit. Statistical analysis was performed with SPSS 11.0.
Results: Serum INSL3 concentrations of male students with each Tanner stage were 0.21 ± 0.13, 0.45 ± 0.28, 1.00 ± 0.74, 1.13 ± 1.33, 2.01 ± 0.90 ng/ml, respectively. Serum INSL3 levels were significantly related to the elevated Tanner stage ($r=0.77$, $p< 0.001$).
Conclusion: Serum INSL3 levels increased consistently with the development of male puberty in Mongolian population of East Asia.

P2-d3-1072 Puberty and Gonads 6

Genetic variants of estrogen receptor beta may cause gynaecomastia in adolescents

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Background: Gynecomastia is a benign breast enlargement in male and affects one-third of adolescent. Estrogen receptors and aromatase enzyme activity may play important roles in the pathogenesis of gynecomastia. Studies on expression of estrogen receptors in patients with gynecomastia have been reported generally in histological analysis. One study showed relationship between estrogen receptor (ER) alpha polymorphism and gynecomastia.
Objective and hypotheses: To evaluate the relations between aromatase gene (CYP19), estrogen receptor alpha and beta gene *polymorphism and gynecomastia.*
Methods: One hundred six male adolescents with gynecomastia and 85 controls were enrolled into the study. The patients who with chronic illness, medication uses, and have syndrome were excluded. Total serum testosterone (T) and estradiol (E2) levels were studied. DNA was extracted from genejet genomic DNA purification kit. We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. We determined alleles and the genotypes of CYP19, ERs alpha and beta gene polymorphism.
Results: Median ages of the study group and the control group were 13.7 (10.1-17.95) years and 14.16 (10.83-17.9) years, respectively. Median level of E2 was 16.86 (2.58-78.47) pg/ml in the study group and 12.41 (5.00-65.40) pg/ml in the control group ($p< 0.001$). Median level of T was 1.46 (0.13-12.02) ng/ml in the study group and 2.19 (0.11-7.04) ng/ml in the control group ($p=0.714$). We found a significant relationship ER beta polymorphism and gynecomastia ($p< 0.001$). There was no association between CYP19 gene polymorphism and gynecomastia ($p>0.05$).
Conclusions: According to our results, increased E level and ER beta gene polymorphism may explain why some adolescent have gynecomastia. Moreover; this study lightened on the profound necessity for further investigations addressing the question of the genetic components of gynecomastia in Turkish population.

P2-d3-1073 Puberty and Gonads 6

Puberty in Chilean boys shows earlier onset of testicular enlargement

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Background: An earlier age of pubertal onset has been described in girls. Whether this phenomenon has occurred in boys is controversial. Most studies have determined age of puberty using genitalia inspection, but few publications have evaluated pubertal development using testicular volume.
Objective and hypotheses: To evaluate the age of onset and presence of precocious puberty/early puberty in a group of Chilean boys. To evaluate differences in the age of onset according to testicular volume and genitalia inspection.
Methods: A pediatric endocrinologist examined 340 children (7-19 years) attending four schools in central Santiago. We assessed pubertal development by testicular volume (TV) and according to Tanner stage (GT) by genitalia inspection. Onset of puberty was diagnosed if testes ≥4ml or GT2 was observed. Precocious puberty and early puberty were diagnosed if testes≥ 4cc or GT2 presented younger than 9 yr and 9-10 yr, respectively. Analysis was performed by Probit and Cox regression.
Results: Onset of puberty occurred at age 10.2±1.5 years by TV and at age 11.1±1.6 years by GT (Table). Precocious puberty was observed in 3 % of boys by GT and 3% by TV. Early puberty was observed in 6 % of children either by GT and TV. BMI z score was not associated with the age of pubertal onset.

Tanner	GT(yr.)	TV(yr.)
2	11.1±1.6	10.2±1.5*
3	12.7±2.7	12.4±2.5
4	13.7±2.7	13.3±2.9
5	15.6±2.1	14.3±2.1

[Table1]
*p=0.0039 Tanner 2 GT vs TV

Conclusions: We observed that testes ≥ 4 cc occurred one year earlier than GT2. These data suggest that testicular enlargement is occurring earlier than Chileans studies performed 10 years ago, but the age that genitalia reach GT2 is similar to what was observed previously. The age of final stages of pubertal development has not been modified during the last decade.

P2-d3-1074 Puberty and Gonads 6

Isolated early thelarche: is it related with ovarian hyperandrogenism?

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Background: To evaluate weather early thelarche and central early puberty is a marker of metabolic risk factors in adolescence.
Materials and methods: 27 girls with a history of precocious puberty were enrolled in the study with a mean age of at least 15 years. The patients were evaluated with physical findings, HOMA-IR, androgen levels and pelvic ultrasonography.
Results: 15 of the patients (55,6 %) were grouped as early pubarche (EP) and 12 of them were grouped as (44,4 %) early telarche (ET). The mean ages were 16,7±0,94 and 17,6±2,7 years respectively. 2 of the patients in the EP and 5 of the patients in ET group were diagnosed as central early puberty (CEP) at follow up and are excluded from the study group. In both of the groups birth weight was not correlated with the onset of puberty (p>0,05). In the EP group as BMI increased the age of menarche decreased and in the ET group as weight SDS increased the age of onset of axillary and pubic hair decreased (p≤0,05). Although children with ET achieved their target height (r:0,78; p:0,003), children with EP achieved their predictive adult height calculated at initial diagnosis (r:0,53; p:0,03). In ET group as BMI SDS and percentage of fat mass increased SHBG and IGFBP 1 decreased. In the EP group as DHEAS and mean volume of the ovaries increased IGF BP1 decreased (p≤0,05).
Conclusion: PT can be a predictor of metabolic abnormalities in adolescence and overweight can be increasing this possibility. PT patients should be followed up for metabolic disturbances and puberty.

P2-d3-1075 Puberty and Gonads 6

Evaluating the efficacy of treatment with a GnRH analogue in patients with central precocious puberty

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Background: There are various approaches to the dose of the GnRH analogue (GnRHa) to be used in treatment of central precocious puberty (CPP).
Objective and hypotheses: The purpose of this study was to evaluate the efficacy of leuprolide acetate used at a dose of 3.75 mg once every 28 days.
Methods: A total of 62 female child patients with a mean age of 7.9±1.3 (4.3 - 10) years, who had been diagnosed with CPP and started on GnRHa treatment (leuprolide acetate, Lucrin depot®, 3.75 mg once every 28 days), were included in the study. The efficacy of treatment was evaluated with anthropometric data obtained, progression of pubertal symptoms observed, as well as GnRHa tests, and when necessary, intravenous GnRH tests carried out in physical examinations that were performed once every 3 months. A peak serum LH level of ≥3 mIU/mL in GnRHa tests, and a peak LH level of ≥2 mIU/mL in GnRH tests were regarded as a non-suppressed Hypothalamic-Hypophyseal-Gonadal (HHG) axis, and in turn, taking other clinical findings into account, the treatment dosages were increased.
Results: In the current study, treatment of early/advanced puberty at a dose of 3.75 mg once every 28 days resulted in the suppression of the HHG axis in 85.5% of the patients, while the dose had to be increased in 14.5% of them.
Conclusions: The findings of this study revealed that a high starting dose of leuprolide acetate may not be necessary in every patient for the treatment of CPP. Starting at a dose of 3.75 mg once every 28 days and increasing it with regards to findings in follow-ups would be a better approach.

P2-d1-1076 Puberty and Gonads 7

Androgen profile and anti-Mullerian hormone levels in girls with premature adrenarche

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Background: Premature adrenarche (PA), the presence of pubic hair before age eight years in girls, is considered a harbinger of polycystic ovary syndrome (PCOS). Anti-Mullerian hormone (AMH), a dimeric glycoprotein, reflects the amount of growing follicles in the ovaries and is considered a robust index of ovarian function. AMH levels are known to be elevated in patients with PCOS and also in pre pubertal daughters of women with PCOS.
Objective and hypotheses: The goal of this study was to determine the androgen and AMH profile in a multiethnic cohort of girls with PA.
Methods: Girls diagnosed with PA between 2002- 2012 were studied for BMI, bone age (BA), testosterone, dehydroepiandrosterone sulfate (DHEA-S) and 17-hydroxyprogesterone (17-OHP). Age matched girls were identified to serve as a comparison group. AMH levels were measured in stored sera of girls with PA as well in matched controls via the AMH Gen II ELISA assay from Quest Diagnostics, Nichols Institute (reference range< 18 years: 0.3-11.2ng/ml).
Results: Fifty-one patients with PA (58% Hispanic) with an average BMI (mean± SD) of 19.4± 4.1years, BA of 6.9± 3.2 years and chronological age (CA) 6.8± 0.8 years were compared to controls (n= 15) with BMI of 16.4±1.56 years, BA of 6.2±1.6 years and CA of 6.02± 1.3 years. Testosterone levels of 11.5± 4.1 ng/dl were elevated in 66% (≤10: pre pubertal) of girls of PA. DHEA-S levels of 67± 56 ug/dl (≥75: 6-8 yr; ≥55< 5 yr) were elevated in 21% of girls with PA, and 40% of all girls with PA had an advanced BA (defined as BA≥ 1 year of CA). In girls with PA (n=14) AMH levels of 2.16±1.7 ng/dl were lower than in controls (n=6) 4.18± 2.58 ng/dl, though this difference did not reach statistical significance (p= 0.128).
Conclusions: In our investigation we did not find PCOS related abnormalities in serum AMH levels in girls with PA. AMH levels cannot discriminate which girls with PA will go on to develop PCOS in the future.

P2-d1-1077 Puberty and Gonads 7

The selected mutations in *KISS1R* gene in patients with GnRH-dependent precocious puberty

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Background: *KISS1R* gene, which encodes kisspeptin receptor, is an important factor playing a crucial role in pubertal development. The activating mutations of *KISS1R* gene can lead to GnRH-dependent central precocious puberty (CPP).
Objective and hypotheses: To analyze the frequency of selected mutations in *KISS1R* gene in patients with CPP
Methods: The study group consisted of 15 patients with CPP (13 girls and 2 boys) aged from 8 months to 8 years. 15 patients with normal time of puberty were recruited as control group.
DNA was extracted from periferal blood lymphocytes. The selected regions of DNA were amplified by polymerase chain reaction (PCR) under optimal conditions, using specific primers. The PCR products were subjected to multitemperature single-strand conformation polymorphism (MSSCP) analysis in 8% polyacrylamide gel.
Subsequently minisequencing was performed to analyze selected mutation in *KISS1R* gene: X399R, R331X(exon 5) and L148S (exon 3)
Results: No mutation in *KISS1R* gene: X399R, R331X(exon 5) and L148S (exon 3) were found in the group of patients with CPP.
Conclusions: Analyzed mutations in *KISS1R* gene are not a frequent reason of CPP. Sequencing of the whole gene would help to find other mutations. The other genes can also contribute to ICPP.

P2-d1-1078 Puberty and Gonads 7

Pubertal pathways and the relationship to anthropometric changes in childhood: results from a prospective JUSAD study

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Background: Maturational timing as a factor in female fatness and obesity.
Objective and hypotheses: To examine the relationship of the initial manifestation of pubertal development in children to anthropometric measurements recorded during the childhood and adolescence.
Methods: The JUSAD study included 1311 females, 10-15 year olds from secondary schools in nine towns of Serbia. Girls with serial self-assessments of Tanner stages of breast and pubic hair developments.
Results: All the girls on the stage of development of puberty in 10. years divided into categories:
I -B1PH1(710/54%);
II-B1PH2(116/9%);
III-B2PH1(199/15%);
IV-B2PH2(286/22%).
(Table 1)

10.years	Weight (kg)	Height (cm)	BMI	Waist circumference (cm)	triceps skifold (mm)	subscapular skifnfold (mm)
I	29,6	135,3	16,0	59	12	7,5
II	29,4	136,5	15,7	57	14	7,4
III	36,3	140,3	18,4	65	15	11,9
IV	35,2	139,9	18	60	16	11,4
15.years						
I	55,6	165,0	22,1	70	15	11,7
II	53,6	164,6	20	69	14	10,8
III	52,9	167	19	67	14	10,3
IV	60,5	165,3	22	73	15	13

[Table 1. Pubertal development in children and ant]

Conclusions: Girls with early thelarche and later adrenarche, have more rapid mean weight gain during the 10. years of life, higher BMI and waist cicumferece, subscapular skinfold, hip circumference during adolescence.

P2-d1-1079 Puberty and Gonads 7

The value of breast and pelvic ultrasonography for the diagnosis of precocious puberty

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Background: The first presentation of puberty in girls is usually breast enlargement; however, pubic hair growth may be the first sign in some cases. Obesity can mimic precocious puberty presenting with findings such as fat deposition in breasts and growth acceleration.
Objective and hypotheses: To evaluate the utility of breast and pelvic ultrasound for the diagnosis of precocious puberty.
Methods: A total of 86 girls between the ages of 6 to 9 years with non-palpable breast gland were recruited for this study. Thirty two subjects were normal weight healthy (Group 1), 23 were obese or over-weight (Group 2), 16 had premature adrenarche (PA) (Group 3) and 15 were obese or over-weight with PA (Group 4). All subjects underwent anthropometric measurements and physical examination. Breast and pelvic ultrasound imaging was done by the same radiologist. Blood samples were taken for LH, FSH, estradiol and bone ages were evaluated.
Results: The average age of the subjects was 7.8±1.1 years and there was no difference in terms of age, ultrasonographic findings and hormone levels between the groups. Although there was no breast enlargement detectable by physical examination, ultrasonographic study revealed a high frequency of presence of breast gland (87.5%, 78.9%, 83.3% and 100%; p>0.05 respectively in Groups 1,2,3 and 4). The rates of increased ovarian volume (≥1ml) (79.2%, 68.4%, 69.2% and 72.7% respectively) and uterine volume (≥1.5ml) (33.3%, 37.5%, 53.8% and 45.5%, respectively) were high and not different between the groups. There was a positive correlation between BMI SDS and bone age (r=0.393, p=0.001) and maximal dimension of uterus (r=0.260, p=0.03) in the whole group. There were also positive correlations between left and right breast volumes and FSH levels (r=0.395, p=0.03 and r=0.397, p=0.03 respectively).
Conclusions: Changes related to puberty can be detected by ultrasound imaging before they become apparent on physical examination.

P2-d1-1080 Puberty and Gonads 7

Clinical presentation and etiology of central precocious puberty in Vietnamese children

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Background: Central precocious puberty (CPP) can cause psychological problem and decrease final height in children. Early diagnosis is important to attain treatment target.
Objective and hypotheses: The aim of this study is to investigate the clinical presentation and the etiology of central precocious puberty in Vietnamese children.
Methods: Cross-sectional method was used in the study. In a period of 1996-2013, 187 children were diagnosed of CPP. Cranial CT or MRI was used to find neurogenic abnormalities.
Results: Male/female ratio was 1/6.5 (25 boys and 162 girls). Admission age was 83.5±29.3 months. Male patients were diagnosed at earlier age of 62.2±34.8 months, compared to 86.8±27.0 months in female patients. In male patients, stretched penile length was 6.9±1.0cm and testicular volume was 6.8±3.2 ml. 80.9% of male patients had pubic hair. In female patients, breast development, pubic hair, and menstruation were seen in 99.4%, 40.1%, and 19.1% respectively. In term of the etiology, 13 patients (6.9%) had brain tumor, among them 9 patients had hypothalamic hamartoma; 2 patient with pituitary tumor; 1 patient with astrocytoma; 1 patient with germinoma. One patient was found to have Rathe's cleft cyst. In our patients' group, 7 patients (3.7%) had CPP due to congenital adrenal hyperplasia (CAH) (6 patients with simple virilisation form and 1 patient with salt losing form). 166 patients (88.7%) were idiopathic. In male patients, brain tumor and CAH occupied 28% and 24%, respectively. In girls, 155/162 patients (95.7%) were idiopathic.
Conclusions: Brain tumor and CAH were important causes of CPP in males.

P2-d1-1081 Puberty and Gonads 7

Epidemiologic study on current pubertal development in Chinese school-aged children

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Objective: To determine the current status of pubertal development of Chinese children.
Methods: A cross-sectional epidemiological study was performed on 18707 children and adolescents aged 6 to 18 years with male/female ratio of 9812/8895 from 6 representative geographical areas, including. Beijing, Tianjin, Hangzhou, Shanghai, Chongqing and Nanning. Using the standard methods, we measured height, weight, waist circumference (WC), hip circumference(HC) and sexual maturation states. Probit analysis was used to calculate the median age and 95% confidence interval (CI) for onset of breast and testicular development.
Results: The median ages of onset of Tanner stages 2 for breast development of girls were 9.69 (95% CI: 9.63-9.75)years. The median age of onset of puberty as indicated by Tanner stages 2 for testicular development of boys was 11.25(95%CI: 11.19-11.30) years. 0.43 %(80/18707) of them was diagnosed

with precocious puberty (43girls and 37 boys) . There was a high prevalence of precocious puberty in the northern region compared with the southwest region (0.736%vs0.282%,p< 0.05). The SD values of BMI and waist-to-hip ratio (W / H) in the precocious puberty children were higher than that of the peer normal children. There was no difference in BMI, waist circumference and waist-to-hip ratio in the precocious puberty children among different regions.
Conclusions: The current diagnostic criteria of precocious puberty is suitable for the children in the survey areas. The prevalences and the onset age of precocious puberty among different regions were different. A positive association between obesity and precocious puberty was found both in boys and girls.

P2-d1-1082 Puberty and Gonads 7

Prepubertal diagnosis of congenital hypogonadotropic hypogonadism by whole-exome sequencing in a neonate with microphallus and cryptorchidism

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Introduction: A common cause of microphallus with or without cryptorchidism in newborn males is GnRH deficiency (congenital hypogonadotropic hypogonadism, CHH). Low serum testosterone (T) levels in the setting of low/normal LH and/or FSH during the minipuberty of infancy are diagnostic clues. Genetic screening has not yet been reported in such cases.
Case study: A boy was born with microphallus and bilateral cryptorchidism without midline defects or other CHH-associated phenotypes. At age 2.5 months he had low T (0.29 nmol/l, normal range: 2.8-12), LH (< 0.5 U/l) and FSH (< 0.5 U/l), yet otherwise normal pituitary function, indicating isolated central hypogonadism. He has a prepubertal sister and the parents are healthy without history of delayed puberty, infertility, or consanguinity. The combination of microphallus, cryptorchidism and isolated central hypogonadism strongly suggests CHH. To confirm the clinical suspicion of CHH, we performed whole-exome sequencing and analyzed the known CHH loci for mutations. We identified a *de novo*, heterozygous mutation in *FGFR1* (c. 1889T>C, p. Leu630Pro) in the proband. This mutation is absent from the 1,000 Genomes database and was previously reported in one female with Kallmann syndrome. It is predicted to be deleterious by 4/5 prediction programs (Polyphen, SIFT, Mutation Taster, ConDel). When mapped to the crystal structure of FGFR1, the L630P mutation is located in kinase domain, makes important hydrophobic contacts with ATP, and is predicted to impair ATP coordination and manifest in a major loss of tyrosine kinase activity of FGFR1.
Conclusion: The presence of a *de novo FGFR1* mutation in our patient strengthens the diagnosis of CHH. Because early diagnosis of CHH can facilitate the age-appropriate timing for hormone replacement therapy to induce puberty, it is tempting to propose genetic testing for all hypogonadal newborns presenting with microphallus and/or cryptorchidism.

P2-d1-1083 Puberty and Gonads 7

Secular trends in growth and sexual maturation among Russian adolescents

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Background: Few studies have examined secular shifts in the tempo of growth and puberty in boys, especially in Eastern Europe.
Objective and hypotheses: To investigate secular trends in growth and sexual maturation among Chapaevsk adolescents during a 14 year period from 1999-2013.
Methods: We compared growth and pubertal development of boys aged 13.5-14.5 years across four cohorts representing different time periods: 1999 (n=478, 13.99±0.29 yrs (mean ±SD), 2008 (n=160, 14.07±0.09 yrs), 2010-11 (n=235, 14.05±0.09 yrs) and 2012-13 (n=199, 13.94±0.18 yrs). For all four groups, the height and weight was measured using the same standard methods. Pubertal status was assessed by Tanner staging of pubic hair (P), genitalia (G), and measurement of testicular volume (TV) using a Prader orchidometer by one investigator (OS). Sexual maturity was defined as G5, TV≥20mL, or P5. Descriptive statistics were computed using SPSS (IBM SPSS Statistics, USA). Age-adjusted, standardized z-scores for height and BMI were calculated using the WHO Growth Standards. T-tests were conducted to compare means in later cohorts to those of 1999.
Results: From 1999-2013, we observed a sequential increase in height and BMI z-scores. The initial negative mean z-scores in 1999 became positive in 2012-13, for both height (-0.18±1.15 in 1999; -0.14±1.17 in 2008, p>0.05; 0.19±1.2 in 2010-11, p< 0.001 and 0.15±1.16 in 2012-13, p< 0.01), and BMI (-0.52±1.13 in 1999; -0.26±1.28 in 2008, p< 0.05; -0.13±1.32 in 2010-11, p< 0.001 and 0.38±1.42 in 2012-13, p< 0.001).The proportion of adolescents who had reached sexual maturity at age ~14 years increased with the year of examination: based on G5, from 5% in 1999 to 38% in 2012-13; for TV≥20mL, from 31% to 54%; and for P5, from 2% to 10%.
Conclusions: These data suggest that there has been a trend towards increased linear growth and BMI, as well as earlier attainment of sexual maturity among Chapaevsk adolescents.

P2-d1-1084 Puberty and Gonads 7

Asymptomatic precocious puberty in children; clinical and laboratory characteristics

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Background: Children with bone-age advancement without any pubertal sign (asymptomatic precocious puberty, asymptomatic PP) were reported (CW Ko, et al, at the Annual Meeting of ESPE, 2012).
Objective and hypotheses: In further study, we found additional children with asymptomatic PP. We analyzed their clinical and laboratory characteristics at the time of diagnosis. And some of them were followed-up prospectively to see their clinical and laboratory changes during 6 months.
Methods: Among children whom visited to predict their final adult heights between July 2007 and February 2013, children with significant bone-age advancement (> 1 year) without any pubertal sign before the age of pubertal onset were enrolled. Their clinical and laboratory data including GnRH stimulation were analyzed retrospectively at the time of diagnosis. Sixteen children with asymptomatic PP were followed-up prospectively.
Results: Fifty-one children with asympomatic PP were enrolled. Male: Female ratio was 1:2.4. Positive result (peak LH>5 IU/L) of GnRH stimulation test was found in 22 out of 51 children (43%). Basal LH (IU/L) of GnRH (+) group was significantly higher than GnRH (-) group in boys (0.67±0.72 vs 0.17±0.14, respectively, p< 0.05). Blood estradiol (ng/dL) of GnRH (+)

group was significantly higher than GnRH (-) group in girls (15.39±13.48 vs 5.91±2.12 IU/L, respectively, p< 0.05). There were no significant differences between groups in height, CA, BA and BMI. Sixteen children with asymptomatic PP were followed upto 6months prospectively. Pubertal signs appeared in 7 out of 16 (43%). Their GnRH stimulation tests were positive in 8 out of 16 (50%) at the time of diagnosis. Interestingly, there is no interval change in GnRH stimulation test during 6 months.
Conclusions: Children with BA advancement without pubertal signs such as brreast budding or testicular enlargement was found. Their clinical courses and mechanisms are not known yet. Large-scaled studies are necessary.

P2-d1-1085 Puberty and Gonads 7

Age at menarche (MA) in chronic diseases: coeliac disease (CD), type 1 diabetes mellitus (T1DM) and growth hormone deficiency (GHD)

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Background: MA is an important indicator of physiological development in women and MA delayed was been associated with chronic illness.
Objective: To investigate predictors and factors at diagnosis that influence MA in chronic diseases.
Methods: A cohort of 391 Italian girls aged 11-24 years with chronic illness was assessed. 245 girls (107 with T1DM, 75 with CD, 12 with both T1DM and CD, 51 with GDH) were included. We investigate their anthropometric data, metabolic status, diagnosis parameters, presence of irregular menses and we compared their MA with healthy italian girls MA.
Results: Mean MA for all girls included is 12.7 ± 1.2 years. MA in different groups was: 12.52 years for girls with T1DM, 12.27 years for girls with CD, 13.52 years in girls with both T1DM and CD, 13.38 years in girls with GHD. In T1DM group a strong positive correlation is also found between menarcheal glycated hemoglobin (HbA1c) and mean HbA1c (p< 0.0001, R 0.54). 36.2% of patients with T1DM or CD or both present menses abnormalities. Girls with irregular menses showed MA significantly delayed than girls with regular cycles.
Conclusions: No differences in MA were observed in Italian girls with CD and T1DM compared to Italian healthy population. Instead patients with GHD and girls with both CD and T1DM showed delayed MA compared to healthy population and to girls with only CD or T1DM. Our data on menarcheal HbA1c and mean HbA1c showed that achieve a good metabolic status can let girls with T1DM reach pubertal stages as healthy peers. Data about menses abnormalities probably show that chronic diseases can predispose young adult age menses abnormalities as delayed puberty although it remains to understand the pathophysiological mechanism.

P2-d1-1086 Puberty and Gonads 7

Clinical and laboratory characteristics of bone age advancement in prepubertal children

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Background: It is certain that genetic factor and multiple hormones are involved in skeletal maturation. Bone age advancement in prepubertal children may lead to earlier puberty and reduction of final adult height.
Subjects and methods: During July to August 2011, we conducted a follow-up examination aged 7 to 9 children, who were part of Ewha Birth & Growth Cohort study, Seoul, Korea, which is a prospective cohort established 2001-2006. Bone age was assessed using Greulich-Pyle method. An index of BA advancement was calculated as bone age divided by chronologic age (BA/CA), and it was classified into tertiles according to sex. We assessed the relationship of bone age advancement and anthropometric characteristics, metabolic components, adrenal and sex hormones using one way analysis of variance.
Results: The study subjects comprised 200 children (106 boys, 94 girls). The mean level of BA/CA in boys was 0.97(±0.15), and in girls was 1.03(±0.14). Height z-score and weight z-score were lowest in the 1st tertile for BA/CA and highest in the 3rd tertile in both sexes. BMI z-score, body fat mass and waist circumference were significantly different between tertiles in boys, but there were no significant difference in girls. In addition, the 3rd tertile had the highest risk for overweight and obesity in boys (1st = 5.56%, 2nd = 10.42%, 3rd = 40.91%, p_{trend}< 0.01), whereas there was no significant difference in girls. In endocrine parameters, there were significant mean difference between tertiles in terms of testosterone, DHEA, androstenedione, IGF-1, and insulin for boys, and androstenedione for girls.
Conclusion: These results showed that obesity and increasing of adrenal hormones were related with bone age advancement in prepubertal children, especially in boys.
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P2-d1-1087 Puberty and Gonads 7

Early pubarche and anti-Mullerian hormone (AMH)

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Background: Although the development of polycystic ovary syndrome (PCOS) is a known phenomenon in obesity there is not any evidence in the literature showing a relationship between AMH in obese prepubertal girls and PCOS.
Aim: To evaluate whether AMH levels in prepubertal obese girls are a predictive marker for PCOS and to investigate the relationship between insulin resistance and AMH.
Materials and methods: 60 girls with premature pubarche or obesity and 20 healthy controls between the ages of 6-9 were enrolled.
Results: Patients were grouped as obese (36,7 % , n=22) (mean age: 7,6±0,9years), early pubarche (46,7 %, n=28) (mean age: 7,62±0,77 years) and early pubarche and obesity (16,6 %, n=10) (mean age: 8,2±0,8 years) and control (n:20 mean age: 7,42±0,88 years) group. Serum AMH levels were not different between the four groups (1,97±1,36; 2,24±1,79; 2,24±1,99 and 2,05±1,5 ng/ml respectively). HOMA-IR index of the obese group and the premature pubarche and obesity group were statistically different than the early pubarche group (p=0,001) Free testosterone and prolactin levels were increased in the early pubarche and obesity group. $DHEASO_4$ levels were increased both in the early pubarche group and early pubarche with obesity group (p< 0,05). When the AMH levels were compared in between the patients with elevated $DHEASO_4$ levels; AMH was increased in early pubarche group.
Conclusion: AMH levels were not different in any of the groups and there was no relationship between AMH and insulin resistance. The number of the patients included in this study is not enough and more studies with increased number of patients are needed to draw a conclusion.

P2-d2-1088 Puberty and Gonads 8

Evaluation of puberty and fertility in French galactosemic patients

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Classic galactosemia is a rare hereditary disorder of galactose metabolism occuring in approximately in 1 for 30000 births. Long-term diet-independent complications consist of premature ovarian failure and cognition sequelae.
As a collaborative work between French Reference Centers of Rare Diseases, we designed a questionnaire completed by biological and sonographic evaluation to
1) evaluate the number of French galactosemic patients,
2) evaluate the gonadal function in men and women,
3) establish recommendations on the management of their puberty and fertility and
4) assess the indications of ovarian preservation.
We report here on currently 101 filled questionnaires, from 45 males and 56 females. Sixty-nine percent of women had a spontaneous puberty with a first stage of breast development appearing at 12 years (n=31) and 25/31 women had spontaneous menarche at 14.6 years (14 women had induced menarche at 17 years old). This is significantly later than in 251 girls from a French cohort who had menses at 12.6 years ($p< 0.01$). Fifty percent of women had secondary amenorrhea. Eleven girls under 16 had an FSH dosage, with an average of 8,1UI/l for girls with spontaneous puberty and 103UI/l, for girls without. Women over 16years old had an average FSH level of 73UI/l. All the pelvic ultrasounds (n=15) showed small ovaries < 0,3cm3 without visible follicles. Four women out of 5 desiring a pregnancy succeeded, ¾ with spontaneous puberty, 2/4 with regular menstrual cycles. Puberty and biological data for men were normal. No men tried to conceive.
Galactosemia is a rare disease and the number of patients in France is estimated around 250. We therefore have currently data on nearly half of the French cohort. These first results show
1) that puberty is often beginning spontaneously, with a rather late timing and
2) confirm premature ovarian failure in the patient. However spontaneous pregnancies do occur and may not be as rare as reported in the literature.

P2-d2-1089 Puberty and Gonads 8

Cytokine profile in girls with early- or precocious puberty

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Background: Both growth in height and gain of weight are accelerated during puberty. They are mainly affected by sex-hormones, growth hormone and IGF-1, and influenced by various factors either directly or indirectly.
Objective and hypotheses: We designed the study to find out the expression of various cytokines in the sera of female children with early- or precocious puberty and to analyze the association between the cytokines and the puberty status.
Methods: Twenty-eight female children with breast budding before 9 years of age, who underwent the LHRH stimulation test as well as cytokine analysis in their blood, were included in this study. The height, weight, and BMI were measured. We defined obesity when the BMI was 95 percentile or more. We also defined puberty state when the maximum LH level was 5 IU/L or more on LHRH stimulation test. The blood levels of adiponectin, leptin, ghrelin, IL-1β, IL-6, IL-10, resistin, and TNFα were measured by Luminex multiple bead technology (Milliplex; Millipore Co., Billerica, MA, Bio-plex; Bio-Rad laboratories, Hercules, CA).
Results: Nineteen out of 28 children were categorized as having early- or precocious puberty. Their mean IL-6 level was lower in pubertal children than that in prepubertal state (4.48±4.77 vs. 19.56±20.26 pg/mL, p=0.057). The leptin and resistin levels were significantly higher in obesity group (n=6) than in non-obesity group, while the ghrelin was significantly lower in obesity group ($p < 0.05$).
Conclusions: The female children younger than 9 years of age in early- or precocious puberty did not show the increment of leptin or resistin compared to female prepubertal children, although the obesity group showed significantly higher levels of leptin and resistin.

P2-d2-1090 Puberty and Gonads 8

Effects of aromatase inhibitors therapy in boys with short stature

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Background: Estrogens have an essential role in the regulation of bone maturation and the closure of growth plates in both sexes.
Objective and hypotheses: This retrospective study was designed to evaluate whether aromatase inhibitor (anastrozole), could delay bone age (BA) acceleration and increase predicted adult height in pubertal boys with short stature.
Methods: Twenty six boys with short stature received aromatase inhibitor (anastrozole), were evaluated retrospectively. Duration of therapy was 8-34 months. Sixteen boys were diagnosed idiopathic short stature. Ten boys had growth hormone (GH) deficiency and they received GH therapy as well. Height standard deviation score (SDS), predicted adult height (PAH), BA, hormone levels and bone mineral density (BMD) were evaluated at before and after treatment.
Results: Height SDS in all boys was significantly increased after treatment (-1.6±0.7), compared to before treatment (-2.3±0.8) (p=0.001). Difference between chronological age (CA) and BA (CA-BA) was significantly increased after treatment 2.1±0.2), compared to before treatment (1.9 ± 1.2) (p=0.002). Significantly increase in PAH was found after treatment (p=0.001). Estradiol levels did not changed before and after treatment.
There was no significant difference on BMD at before and after treatment (p>0.05).
Conclusions: Aromatase inhibitors (anastrozole) therapy may delay bone maturation and closure of growth plates. Aromatase inhibitors seems to be effective in increasing adult height of boys with both idiopathic short stature and GH deficiency, while maintaining normal pubertal progression.

P2-d2-1091 Puberty and Gonads 8

McCune-Albright syndrome: clinical presentation and progression of symptoms in children

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Background: McCune-Albright syndrome (MAS) is a rare sporadic disease with three characteristic features, fibrous dysplasia (FD), café-au-lait spots and peripheral precocious puberty (PPP) associated with hyperfunctioning endocrinopathies. The broad spectrum of manifestations occurring alone or in combination throughout life reflects the mosaic distribution of GNAS-activating somatic mutations in various tissues. Little is known about the course of disease in childhood.
Objective: To describe initial presentation and progression in children with MAS.
Population and/or methods: The medical records of children (26 girls, 5 boys) with MCA diagnosed at two pediatric endocrinology centers in the last decade were retrospectively reviewed.

Results: Most girls (*n*=24; 92%) presented with clinical signs of PP (breast developpement *n*=24, vaginal bleeding *n*=20) at median age of 2.98 (2.50-5.79) years. At initial evaluation, girls (*n*=26) had one (PPP *n*=10, skin n=1), two (PPP+skin *n*=7), or three (PPP+skin+FD *n*=7, skin+FD+Cushing *n*=1) signs, with additional signs including hyperthyroidism (*n*=3), PPP (*n*=1), phosphate wasting (*n*=2), FD (*n*=6) and GH excess (*n*=1) at last evaluation, at median age of 8.80 (4.45-11.61) years. Drug treatment, mostly aromatase inhibitors, was introduced after first (*n*=7 with accelerated GV *n*=4), second (*n*=1) or third (*n*=12) episode of vaginal bleeding. Central PP occurred during treatment in two cases. All boys (*n*=5) initially presented with bone and skin lesions, at median age of 8.48 (7.84-8.77) years. By the age of 15.29 (13.81-17.00) years, one boy also displayed hyperthyroidism and phosphate wasting.
Conclusions: PPP is more frequent in girls than boys and allows early detection of MAS, which has an extremely heterogeneous phenotype, with only one clinical feature initially present in many cases. Recurrent vaginal bleeding should identify more aggressive forms requiring treatment. The risk of progression to central PP necessitates careful follow-up.

P2-d2-1092 Puberty and Gonads 8

Hypothalamic pituitary testicular axis maturation among lean and overweight boys

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Background: There is scarcity of data on the impact of over weight/ obesity on pubertal development in boys.
Objective and hypotheses: To assess pubertal development and hypothalamic pituitary testicular (HPT) axis of lean and over weight children.
Methods: Boys in the age group of 5 to 18 years were the subjects for this study. Children with any chronic illness or on medications which affect growth/ glucose tolerance were excluded. All children underwent detailed physical examination. Blood was collected after overnight fast for glucose, insulin, LH, FSH, Testosterone, Prolactin, T4 and TSH. LH, FSH,Testosterone, estradiol, TSH,T4,PTH were analysed by ECLIA (Cobas E411). International Obesity Task force (IOTF) criteria was used for classification of over weight and obesity. Study protocol was approved by institute Ethics committee.
Results: Thirty two lean and 47 overweight boys were enrolled for this study. The age at onset of puberty were comparable but the tempo of pubertal maturation was slower in the over weight group group. Serum testosterone for a given testicular volume was lower among the overweight children. Between 14 and 18 years, mean testicular volume was comparable (19±7.03 vs 19.28±5.9 ml) in the 2 groups, but testosterone was significantly lower (5.75±2.75 vs 2.99±2.4 ng/mL) in the overweight boys. There were 8 boys more than14 years of age who had significant gynecomastia, delay in progression of puberty, lower testicular volume & testosterone with FSH and LH in the low normal range. They had higher BMI, fasting insulin and higher TSH with T4 in the normal range.
Conclusions: The age at onset of puberty was comparable in lean and over weight boys. There was dissociation between testicular volume and plasma testosterone in over weight boys.

P2-d2-1093 Puberty and Gonads 8

Precocious puberty in Turner syndrome

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Introduction: Turner syndrome (TS) is a common chromosomal disorder caused by complete or partial X monosomy affecting approximately 1:2,500 live-born females. A few rare cases of precocious puberty have been reported in patients with mosaic TS. We report the first case of precocious puberty in a mosaic Turner syndrome with a ring X chromosome.
Case study: An 8-year-old girl was referred to pediatric endocrinology outpatient clinic with growth concerns. She was born at term, weighing 2200g and had an unremarkable past medical history. Her height was 117.8 cm (less than 3rd percentile on a Korean standard growth chart), and weight was 24.8 kg (10-25th percentile on a Korean standard growth chart). A physical examination demonstrated Tanner breast stage II.Chromosome analysis revealed a karyotype, 46,X,r(X)(p22.2q22.3)[11]/45,X[9]. FISH analysis excluded Y-chromosome-specific sequences. There were no other associated abnormalities on echocardiography and kidney ultrasonography.Endocrine evaluation revealed FSH levels 4.0 mIU/mL, LH levels 1.0 mIU/mL, estradiol levels 10 pg/mL, and IGF-1 levels 166.1 ng/mL. Thyroid function tests were normal.Skeletal maturation, evaluated by a left wrist x-ray was 7 years and 10 months.After confirmed diagnosis as mosaic TS, growth hormone (GH) treatment was started. After one year, a physical examination demonstrated Tanner breast stage III. Because her pubertal development progressed and she showed short stature, GnRH analogue therapy was added, in order to slow pubertal progression and to preserve maximum adult stature.
Conclusion: We report the first case of precocious puberty in a mosaic TS with a ring X chromosome. Precocious puberty in TS patients is very rare and six cases have been reported. This case is the first report of precocious puberty in TS with a ring chromosome.

P2-d2-1094 Puberty and Gonads 8

Let's simplify the diagnosis of precocious puberty

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Background: The incidence of precocious puberty (PP) has risen in recent years. The diagnosis of PP is clinical and the determination of etiology depends on laboratory tests and imaging. Therefore, the speed and accuracy of laboratory tests are important for therapeutic success. The stimulation test with GnRH (LHRH) is currently the choice of laboratory tests for differentiating between true precocious puberty, peripheral precocious puberty and thelarche. However, this test depends on the hormonal intravenous administration of a GnRH agonist raising the final cost of the exam.
Objective and hypotheses: This study seeks to identify a cutoff in basal LH (Luteinizing Hormone), without stimulation, which could predict positive response to GnRH stimulation test.
Methods: Between 2006 and 2013, we performed 975 tests with GnRH stimulus. Of these, 392 were performed in children with clinical criteria of early puberty. We determined serum levels of LH in basal and GnRH-stimulated in 846 girls and 129 boys.
Results: 104 girls aged up to 8 years tested positive for precocious puberty and 06 boys with age until 9 years also showed puberty levels of LH after stimulation. This study demonstrated that basal LH levels above 0.42 mIU / mL in girls showed 54.3% sensitivity, 90.3% specificity and 79.6% accuracy for the diagnosis of true puberty . In boys, basal LH levels above 0.69 mIU / mL has 80% sensitivity, 96.3% specificity and 91.9% accuracy for the diagnosis of true precocious puberty.
Conclusion: Basal LH levels above 0.42 mIU/mL for girls and 0.69 mIU/mL in boys are indicative of activation of the gonadotropic axis and may corroborate to confirm diagnosis and indicate the begin of therapy for true precocious puberty, without the need of intravenous administration of a GnRH agonist and performing a multiple sample hormone curve.

P2-d2-1095 Puberty and Gonads 8

The relationship between serum vitamin D levels and precocious puberty in children

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Background: Recently, the facts that age at menarche is associated with vitamin D deficiency and 1,25-dihydroxyvitamin D3 regulates estrogen metabolism process are reported. However, the relationship between the precocious puberty and vitamin D levels has not been studied yet. In this study, the association of 25-hydroxy vitamin D3 levels with precocious puberty was evaluated.
Methods: Girls under the age of 9 visited the hospital with a diagnosis of precocious puberty(n=150) as well as with healthy patients of similar age without breast engorgement(n=30) were measured Serum 25(OH)D concentrations from April 2012 to August 2012.

Results: There are significant differences in the median value of 25-hydroxy vitamin D concentration between the precocious puberty group (17.73±4.34 ng/mL) and the control group (21.4±5.08 ng/mL) ($p < 0.05$). And also, there are significant differences in Serum 1,25(OH)D concentrations between the precocious puberty group (47.38±12.38 pg/mL), and the control group (54.75±20.79 pg/mL) ($p < 0.05$). 68.67% of precocious puberty girls were vitamin D-deficient (25-OH-D< 20 ng/mL) and 31.33% had insufficiency value (≥20 and < 30 ng/mL). 43.3% of control groups were vitamin D-deficient, 50.0% had insufficiency value, and 6.7% were sufficient. There was significant difference in the prevalence of precocious puberty between the two groups, vitamin D-insufficient or sufficient group and deficient group (Univariate analysis, $p< 0.05$,Odds ratio 2.866). In a multivariate analysis after adjustment for chronological age, bone age, LH, FSH, estradiol, their relationship between vitamin D and precocious puberty was not increased ($p>0.001$).
Conclusions: These results showed that serum 25-hydroxy vitamin D levels were associated with precocious puberty, but it is difficult to think of as a cause of precocious puberty. For further research, the number of the control group should be increased.

P2-d2-1096 Puberty and Gonads 8

Changes of the predicted adult height after gonadotropin-releasing hormone agonist treatment in girls with idiopathic true precocious puberty

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Objective and hypotheses: We evaluated the effects of the time to start treatment with gonadotropin-releasing hormone agonist(GnRHa) on the change of predicted adult height(PAH) in idiopathic true precocious puberty girls(TPP).
Methods: In this retrospective study, we collected data on the 104 girls with TPP [60 diagnosed before chronological age of 8 year(Group 1); and 44 between 8 and 9 year(Group 2)] who treated with GnRHa over 18 months, from January 2002 through March 2012.
Results: Difference was found in PAH SDS before and after treatment (-1.91±1.47 vs. -1.37±1.17 after 1 year treatment, -1.96±1.58 vs. -0.48±1.11 after 3 years treatment) in total patient. The difference of bone age and chronologic age was decreased with GnRHa treatment. The difference between mid-parental height SDS and PAH SDS was decreased after GnRHa treatment. PAH SDS minus mid-parental height was changed from -1.49±1.44 to -0.96±1.10 years in total patients, from -1.72±1.45 to -1.08±1.09 in Group 1, from -1.18±1.37 to -0.78±1.10 in Group 2 after 1 year treatment (P< 0.001); from -1.51±1.40 years to -0.44±0.98 in total patients, from -1.66±1.51 to -0.57±1.03 in group 1, from -1.27±1.22 years to -0.26±0.87 years in group 2 after 3 years treatment(P< 0.001). But the means of PAH SDS couldn't go beyond mid-parental height SDS.High PAH gain after 1 year treatment was positively correlated with the height at start(r=0.64, P< 0.01 in Group 1, r=0.36, P=0.02 in Group 2) and mid-parental height (r=0.40, .P< 0.001 in Group 1, r=0.34, P=0.02 in Group 2).The body mass index SDS was increased after 1 year treatment in two groups, and decreased after 3 years treatment. But this change wasn't statistically significant.
Conclusions: GnRHa treatment can preserve growth potential by slowing bone age progression, resulting in short adult height. But it can't alter the genetic growth potential.

P2-d2-1097 Puberty and Gonads 8

Near-final height and time of menarche in girls with idiopathic central precocious puberty after gonadotropin-releasing hormone agonist treatment

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Purpose: Idiopathic central precocious puberty (ICPP) is treated with GnRH agonist (GnRHa) to stabilize secondary sexual characteristics and to prevent loss of final height (FH) due to accelerated bone maturation. But long-term outcome data about final height or hypothalamic-pituitary- gonadal axis reactivation of ICPP girls treated with GnRHa are conflicting. Some studies suggest that FH is not always improved and that treatment may induce excessive weight gain. We, therefore, analysed near-final height and time of menarche of girls with ICPP who had GnRHa therapy.
Methods: Achieved height due to therapy and time of menarche was assessed in 41 girls with ICPP treated with GnRHa over 1 year. Near-final height (NFH) was measured after menstruation starts, and at least one year has elapsed.
Results: Mean age of GnRHa-treated girls was 8.6±0.6 years at the start of treatment. Mean duration of GnRHa treatment was 1.7±0.5 years. At start of treatment, the mean chronological age (CA) of girls was 8.6±0.6 years and bone age (BA) was 10.3±0.8 years. The height SDS adjusted for CA decreased from 1.16±0.84 at the onset of treatment to 0.87±0.80 at the end of treatment. However, the height SDS adjusted for BA increased from -0.43±0.62 at beginning of treatment to -0.18±0.52 the end of treatment. Near-final height at the age of 14.1±1.2 years was 160±3.7 cm (0.52±0.69 SDS). Near-final height gain over pre-treatment predicted adult height was 2.5±1.7 cm. Menarche occurred after GnRHa therapy discontinuation for 1.3±0.5 years (range 0.3-2.9 years) at the age of 12.1±0.7 years.
Conclusion: GnRHa therapy exerts beneficial effect on near final height by slowing bone maturation. There are no detrimetal effects on hypothalamic-pituitary-gonadal axis function after treatment.

P2-d2-1098 Puberty and Gonads 8

Outcomes of pubertal development as a function of pubertal onset age

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Background: The onset of girls' puberty represents critical levels of estrogen and androgen, but the duration and conclusion that make a girl reproductively mature.
Objective and hypotheses: The onset age of puberty impacts on its progress, pubertal growth and transition to adulthood.
Methods: We analyzed prospectively collected data of 659 girls from 1991-2006, considering the onset of puberty (B2 and P2), menarche age [M], transition to adulthood (B5 and P5) and pubertal growth. Data were divided into quartiles (Q) by B2 age, and we compared 1stQ (B2 age 8.95±0.03[SD]) with 4thQ (10.74±0.60y, P< .001; mean difference 1.79y) for puberty's duration and completion parameters.
Results: 1stQ for B2 girls had their P2 at age 9.81±0.65 and 4thQ at 10.74±0.77y, resp.(P< .001, diff 0.92y), and M at 11.91±1.18 and 12.99±1.12y (P< .001; mean diff 1.08y). Thus, P2 lagged behind B2 by 0.86±0.65 for B2-1stQ girls, but it was 0 (±0.79) for 4thQ.
The duration from B2 to M was longer for B2-1stQ girls (2.95±1.19) than 4thQ (2.26±1.03, P< 0.001; diff 0.69y). The completion of breast development (B5) was at age 13.96±0.96 and 14.40±0.84y for 1st and 4thQ, (P< 0.001, diff 0.44 y), whereas P5 occurred at 13.74±0.96 and 14.39 ±0.8y, (P< 0.001, diff 0.65y).
The duration B2 to B5 was longer in 1stQ girls (4.71±0.97y) than 4thQ (3.66±0.87y, P< 0.001, diff 1.05y) but P2 to P5 was comparable (NS). During B2-B5, 1stQ girls grew more (24.8±5.5cm) than 4thQ (19.9±4.5cm, P< 0.001),

yet they reached similar final adult height 164.5±6.4cm.
The duration from M to B5 was comparable between 1st and 4thQ (mean 1.69 and 1.47y, NS).
Conclusions: Early thelarche predicts earlier pubarche >> earlier M, suggesting that B2 may not represent HPG maturation. Puberty duration difference is established by M, with no impact for the interval from M to adulthood. Parents may be reassured that early B2 girls within the normal range have longer puberty, comparable final height and M only three years later.

P2-d1-1099 Sex Differentiation 3

Turner syndrome karyotypes without a short arm (p) pair are associated with more severe dysmorphism and ENT morbidity

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Background: Turner syndrome (TS) is associated with specific physical features & ENT problems.
Hypothesis: 45,X monosomy or 45,X mosaicism with loss of a short arm (p) pair results in more severe dysmorphology & greater ENT morbidity.
Methods: A review of data collected in a prospective randomised controlled TS growth study. Variables examined were
1) karyotype;
2) dysmorphology index (DI) quantifying presence & severity of 14 associated features eg cubitus valgus, short metacarpals; max. score 28, ≥10 arbitrarily chosen to signify severe dysmorphism;
3) ENT morbidity score (ENT) quantifying problems eg recurrent infection, deafness & interventions eg ventilation tubes, mastoid surgery; max. 16.
Results (median [range] unless otherwise stated): At enrolment 103 girls were aged 9.9 [7.0-13.6] years. DI was 5 [0-18]; 17 girls ≥10. Fifty girls had recurrent infections & 33 reported episodes of deafness. Thirty had adenoidectomy &/or tonsillectomy & 42 had ventilation tube insertion (uni/bi-lateral/repeated). No mastoid surgery was reported & 11 had hearing aids. Spearman's (rho) correlation between DI & ENT was 0.39 (p=0.01). Data were stratified, where possible, for karyotype 1) loss of short arm (p) pair eg 45,X; 45,X/46,XiXq (n=49) or 2) retention of short arm (p) pair eg 45,X/46,XX; 45,X/47,XXX; 45,X/46,XY (n=48) & analysed further (Mann-Whitney/Fisher's exact tests).

	DI	Recurrent infections n (%)	Ventilation tube n (%)
Loss of short arm (p) pair	7 [1-18]	33 (67.3)	26 (53.1)
Retention of short arm (p) pair	5 [0-18]	16 (33.3)	14 (29.2)
p	0.0002	0.001	0.02

[Table: DI & ENT according to karyotype]

The 17 severely dysmorphic girls had an ENT score of 6 [2-9] of whom 3 retained a short arm (p) pair.
Conclusions: Recurrent ENT problems & surgery were significantly more likely in girls without a short arm (p) pair in their karyotype. While few were severely dysmorphic, 82.4% of girls who were had no short arm (p) pair & all had ENT involvement. These findings will have implications for ENT surveillance.

P2-d1-1100 Sex Differentiation 3

Childhood androgen treatment effects on body composition and bone density in boys with Klinefelter syndrome: results of a two-year, placebo-controlled clinical trial

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Background: Klinefelter's syndrome (KS) is a genetic disorder defined by karyotype 47,XXY. The physical phenotype includes decreased muscle tone/mass, increased fat mass, and osteoporosis and may result from testicular failure/androgen deficiency in childhood. Androgen replacement is standard in adolescents/adults, but has not been used earlier in childhood in KS. This clinical trial evaluated the effects of childhood androgen replacement on the KS physical phenotype.
Objective: We hypothesized that androgen treatment for two years (y) would have positive effects on body composition, including muscle mass, body fat, and bone density.
Methods: Double-blind, placebo-controlled clinical trial (NCT00348946 [2005-2011]) randomized 93 boys with KS (4-12y), to oxandrolone (Ox [0.06 mg/kg/d], N=46) or placebo (Pl, N=47) for 2y. Study visits (every 6 months) included measurements of limb circumference, body fat % by skin fold, BMI, weight, and bone age X-rays. Cortical bone mass was determined by use of the bone health index (BHI, Visiana). Statistical analyses included repeated measures ANCOVA.
Results: 93 patients enrolled and 86% completed the 2y study. Mean ages at 2y were (Ox) 9.1±2.1y vs. (Pl) 10.2 ±2.6y, P=0.03; the Ox group was slightly younger. Weight SDS but not BMI SDS increased more (change from baseline [BL]) in Ox (0.3±0.6) vs. Pl (-0.1±0.4), P< 0.05. Fewer boys had body fat >25% in Ox (23%) vs. Pl (49%), P=0.03. Increased muscle mass was associated with increased lower leg circumference SDS in Ox (0.5±0.7) vs. Pl (0.1±0.5), P< 0.01. Bone mass, as shown by BHI SDS change from BL, increased more in Ox (0.4±0.7) vs. Pl (-0.2 ±0.6), P < 0.01.
Conclusions: This unique clinical trial demonstrates that childhood Ox treatment for 2y is associated with increased muscle mass, lower percent body fat, increased bone cortical thickness, and no effect on BMI. Gradual age-appropriate androgen replacement in childhood should be considered to optimize body composition in KS.

P2-d1-1101 Sex Differentiation 3

Major determinants and prediction of height development in Turner syndrome patients treated with recombinant human growth hormone

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Background: Recombinant human growth hormone (GH) is commonly used to treat the short stature associated with Turner syndrome (TS). However, the variability in response among patients suggests that individualization is needed in order to optimize growth.
Objective and hypotheses: To identify the major determinants of adult height in TS patients treated with GH.
Methods: 54 girls with TS treated with GH from the age of 10±3 years and for 5±3 years were followed until adult height. The parameters chosen as response variables were adult height (AH), total height gain (THG) and gain over the predicted adult height without treatment (PAH). A multivariate analysis was performed to identify the height influencing variables.
Results: The AH achieved by our patients was 152,9±5 cm, while the gain above the PAH was 5,5±5,4 cm. 63% of our patients reached a normal AH (≥ 151cm, -2 SDS for the normal population). The AH and the gain over the PAH were influenced, in order of importance, by the baseline height (positive correlation), the baseline age (negative correlation) and the first year height velocity (positive correlation). The THG was influenced by the baseline age (negative correlation), the first year height velocity (positive correlation), the baseline bone age/chronological age ratio (negative correlation) and by the age at onset of puberty (positive correlation). We also created a model that allows prediction of THG from variables available at an early stage of the treatment.
Conclusions: Our study supports the importance of the early initiation of GH therapy and of the first-year response. The model we developed can be a useful tool for clinical practice, allowing an accurate prediction of the patient's adult height from her baseline and first year characteristics.

P2-d1-1102 Sex Differentiation 3

Secular trends on birth parameters and pubertal timing in girls with Ullrich-Turner syndrome

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Background: Secular trends (ST) in growth and time of puberty are observed in general populations; however, it is unclear whether similar trends occur in patients with Ullrich-Turner Syndrome (UTS).
Objective and hypotheses: To assess STs in patients with UTS and to evaluate whether clinical management of girls with UTS has changed over time.
Methods: All girls with UTS from the German KIGS database (n=452) were included (312 with induced and 140 with spontaneous puberty). Birth-weight (BW), birth-length (BL), height SDS, and age at start of growth hormone therapy (GHT) and at start of puberty were analysed in four time-intervals which were defined by year of GH start (1986-90; 1991-95; 1996-2000; 2001-2005).
Results: BW-SDS but not BL-SDS showed a positive ST (table). At the start of GHT, height-SDS did not differ over time, but a trend to start GHT at younger age was observed. Height-SDS at start of puberty increased over time. Age at start of spontaneous puberty did not change over time (mean age at thelarche 12.8±1.7), but there was a ST for age when puberty was induced. Duration from thelarche to menarche was relatively short in patients with pubertal induction.

GHT start years	1986-90	1991-95	1996-00	2001-05	p-value
BW-SDS	-1.50	-1.31	-0.99	-1.05	<0.01
BL-SDS	-0.76	-0.51	-0.35	-0.49	n.s.
Age (yrs) (GHT start)	11.4	10.2	9.0	9.7	<0.01
Ht-SDS (GHT start)	-3.31	-3.26	-3.06	-3.05	n.s.
Δ Ht-MPH SDS (GHT start)	-3.19	-3.17	-2.93	-3.06	n.s.
Ht-SDS (PS)	-1.74	-1.48	-1.36	-1.38	<0.01
Δ Ht-MPH SDS (PS)	-1.66	-1.45	-1.19	-1.29	<0.01
Age (puberty induced; yrs)	14.3	13.7	13.5	13.3	<0.01
Duration thelarche-menarche (yrs)	1.2	1.7	1.3	1.1	n.s.

[BW-bir wt,BL-bir len,Ht,MPH-mid par ht,PS-pub star]

Conclusions: STs only for BW-SDS and height SDS at start of puberty were observed. We confirmed that time of GH therapy start and induction of puberty changed with a clear trend towards younger ages. The short time interval from thelarche to menarche requires discussion on management of pubertal induction.

P2-d1-1103 Sex Differentiation 3

Liver function test abnormalities begin early in life in Turner syndrome

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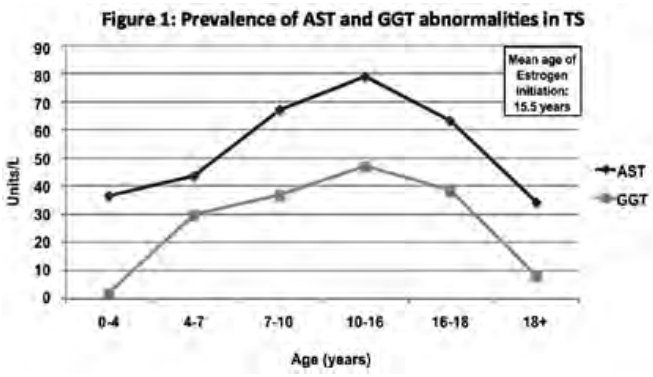
Background: Abnormal liver function tests (LFT: Aspartate Aminotransferase [AST]; Alanine Aminotransferase [ALT]; gamma-glutamyl transpeptidase [GGT]) occur in 20-80% of Turner syndrome (TS) patients (1).
Objective: Determine the prevalence of abnormal LFT in a pediatric TS population followed in a multidisciplinary TS clinic.
Methods: Retrospective chart review of 116 TS patients under the age of 18 year (yr), with clinical LFT measures. Prevalence and 95% confidence intervals (CI), categorized by age group, were estimated with generalized linear models to account for multiple tests per patient.
Results: Mean age was 9.8 +/- 0.26 years. Overall prevalence of LFT anomalies in the 0-10 yr age group was 69% (95% CI: 64 to 74%) and 81% in the 10-16 age group (75 to 87%). AST anomalies were seen at all ages, with the highest prevalence, 79% (CI: 73 to 85 %) in the 10-16 yr age group. GGT anomalies were also observed after age 4 yr and were abnormal in 47 % (CI: 37 to 60%) of the 10-16 yr age group. A decline in the prevalence of abnormal LFT was seen following initiation of estrogen replacement therapy at mean of 15.5 yr (Figure).



[Table 1]

Conclusion: Abnormalities of LFT are common in the pediatric TS population, occurring at a younger age than previously reported. This indicates that LFT changes in TS may have a congenital basis. Estrogen therapy may be protective against liver disease. Additional studies to elucidate etiology and clinical significance are underway.

P2-d1-1104 Sex Differentiation 3

What features predict the development of cholesteatoma in Turner syndrome?

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Background: Middle ear problems are common in Turner syndrome (TS) with development of cholesteatoma in a significant minority.
Aims: To identify
1) risk factors that might lead to the earlier detection of cholesteatoma in TS &
2) any surgical differences in cholesteatoma surgery between girls with & without TS.
Methods: Girls with TS & cholesteatoma were identified from the population of patients who have attended a supra-regional dedicated Turner clinic. Each index case was compared with three age-matched girls with TS without cholesteatoma.
Results (as median [range] unless otherwise stated): Cholesteatoma occurred in 7 (3.9%) of 179 girls attending the TS clinic between 1989 & 2012 inclusive, affecting 9 ears, with recurrence in one girl. Karyotype in the cholesteatoma group was restricted to 45,X (4) or 45,X/46,X,i(Xq) (3). Age at first cholesteatoma presentation was 12.5 [7.5-15.2] years with otorrhoea for 1.3 [1-4] months in 8/10 cases. Comparisons were made between the cholesteatoma & comparison groups using Fisher's exact test. Cholesteatoma ears had a significantly higher proportion of acute & recurrent otitis media (OM) ($p=0.0003$ and 0.0014 respectively) & of OM with effusion ($p=0.0132$), with particularly high proportions of chronic suppurative OM ($p=0.0003$), chronic perforation ($p=0.0005$) & tympanic membrane (TM) retraction ($p< 0.0001$). At surgery, 3/9 cholesteatoma ears showed dehiscent facial nerves, one had undissectable residual disease initially & another required revision mastoidectomy.
Conclusion: Cholesteatoma has a very high prevalence in TS compared to the general population. Affected girls are typically older with a history of chronic middle ear disease & perforation, TM retraction & persistent otorrhoea. We recommend close ENT surveillance in girls with TS who have TM retractions & perforation, with urgent referral for those whose otorrhoea persists > 2 weeks to an ENT specialist who is aware of the potential surgical challenges in these cases.

P2-d1-1105 Sex Differentiation 3

The outcome of prenatal identification of a sex chromosome abnormality

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Introduction: Prenatal diagnosis (PND) via amniocentesis or chorionic villus sampling may result in the identification of a sex chromosome abnormality, often as an incidental finding.
Aims: To ascertain the incidence of sex chromosome abnormalities detected by prenatal diagnosis in the Grampian and the West of Scotland (WoS) regions and to determine the characteristics and outcomes of these cases.
Methods: Retrospective review of all cases of prenatal diagnoses that revealed a sex chromosome abnormality between 2000 and 2012.
Results: Over the period of 12 years, 166 positive cases were identified. The indication for PND was an abnormal ultrasound scan in 95(57%), high-risk first trimester screening results in 31(19%), age related aneuploidy risk in 24(14%), maternal anxiety in 9(5%) and a family history of a chromosomal abnormality in 7(4%). Of the 166 cases, 79(48%) cases were 45,X, 24(14%) were 47,XXY, 14(8%) were 48,XXX, 9(5%) were 45,X/46,XX,, 8(5%) had a structurally abnormal X chromosome, 7(4%) were 45X/46XY, 6(4%) were 48,XYY, 2(1%) were 46,XX/46XY and 17(11%) had other variations of sex chromosomes. Of the 166, 73(44%) pregnancies were terminated and of these cases, 47(64%) had a karyotype of 45,X. An additional 7 pregnancies(4%) were associated with an intrauterine death and 5 of these were 45,X. Based on a combined birth rate of 40,000 births per year for these regions, it is estimated that there was one positive case for 3,500 births and approximately half of these led to a live birth.
Conclusions: 1:7000 births are associated with a prenatally diagnosed sex chromosome abnormality. 45,X is the most commonly encountered abnormality. Given the rare incidence, there is a need to improve our understanding of the care of these cases during the pregnancy as well as afterwards.

P2-d1-1106 Sex Differentiation 3

A rare cause of delayed puberty

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Introduction: Puberty is considered delayed when it has not yet occurred at an age that is 2 to 2.5 SD later than average (13 years in girls).
Case study: A 15-year-old female was referred to our department for DP, primary amenorrhea (PA) and dysmorphisms (cubitus valgus, palpebral ptosis, short neck, truncular obesity and broad chest). Auxological parameters were normal and she was prepubertal. Laboratory and instrumental finding showed ovarian failure with hypoplastic uterus and ovaries. She also presented mental retardation (QI 56). The cytogenetic analysis showed de novo unbalanced X;10 translocation karyotype 46,X,der(X)t(X;10)(q21.31;q22.1). Late replication studies on fibroblast, showed inactivation in 100% of cells studied of the most part of the aberrant chromosome but, interestingly, with a remaining activity of about 30% of translocated terminal part of the chromosome 10 .
Conclusion: We describe the first case of DP, PA, trisomy of 10q22.1-10qter and monosomy of Xq21.31-Xqter owing to de novo unbalanced X;10 translocation. Of interest, despite the partial X monosomy, it is the absence of short stature because the deletion doesn't affect the pseudoautosomal region 1 (PAR 1) implicated in height development. The X deletion we describe involves an important locus for the ovarian function (Xq 27.3: Premature Ovarian Failure 1 gene) that could explain DP. The peculiarity of our case is the presence of DP and PA instead of secondary amenorrhea, as described in another case with similar kariotype, or of premature ovarian failure, as described in cases with mutations in this locus or with partial Xq monosomy. Finally, as other dysmorphisms and mental retardation are probably explained by the partial chromosome 10 trisomy, we are planning to study by real time PCR which genes of the 10 chromosome translocated remain active to try to suggest a more precise phenotype-genotype correlation.

P2-d1-1107 Sex Differentiation 3

Dynamics of parameters of bone remodeling in girls with Turner syndrome on the background of treatment with recombinant growth hormone

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Background: Patients with Turner's syndrome (TS) develop osteoporosis, resulting from estrogen deficiency by gonadal dysgenesis.
Objective and hypotheses: The aim of this study was to assess bone mineral density and parameters of bone remodeling during somatropin therapy in girls with TS.
Methods: We examined 26 girls with Turner's syndrome at the age of 12-15 years, not obtaining estrogens (group 1) and 13 naïve treatment girls with Turner's syndrome of the same age (group 2). Ultrasound osteodensitometry was performed. Levels of osteocalcin, C-terminal telopeptide of type 1 collagen (CTX) were determined in blood serum by ELISA-method before treatment and 6 and 12 months after beginning of somatropin therapy. Somatropin «Rastan» (Pharmstandart, Russia) was prescribed daily at a dose of 0.05 mg/kg subcutaneously. Statistical significance of parameters before and after treatment was evaluated by Wilcoxon single-rank test.
Results: In groups 1 and 2, the median Z-score was -1.9 and -1.8, respectively; osteoporosis was revealed in 3 (11.5%) and 1 (7.7%) girls, respectively, osteopenia - in 6 (23.1%) and 4 (30.8%) girls, respectively. In group 1 before treatment the median of the osteocalcin level was 61.5 ng/ml, the median CTX - 1.11 ng/ml. In this group, after 6 months of somatropin treatment median of the osteocalcin level was increased to 124.0 ng/ml ($p < 0.001$), after 12 month - to 166.1 ng/ml ($p < 0.001$). The median NTX after 6 months of treatment was 1.62 ng/ml ($p < 0.001$), after 12 months - 1.98 ng/ml ($p < 0.001$). The median Z-score rose from -1.9 to -1.8 after 6 months ($p > 0.05$) and to -1.6 after 12 months ($p < 0.019$). In group 2, changes of parameters of bone remodeling and Z-score at follow-up were statistically non-significant.
Conclusions: In girls with Turner's syndrome during of somatropin therapy, osteosynthesis increases more essentially than the bone resorption, which promotes an increase of bone mineral density.

P2-d1-1108 Sex Differentiation 3

A 45,X male patient with 7q distal deletion and rearrangement with SRY gene translocation; a case report

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Background: Chromosomal rearrangements involving SRY gene are rare and may result in different phenotypes. Here we present a male newborn with multiple congenital anomalies whose karyotype was 45X, without any mosaicism.
Case report: Three-month old boy was hospitalized for respiratory distress, hypertension and multiple congenital abnormalities. His birth weight was 2350 g (3-10. percentile), length 42 cm
(< 3. percentile), and head circumference was 32 cm (< 10. percentile). He had microcephaly, cleft lip and palate, low-set ears with large earlobes, anal stenosis and accessory nipple. His external genitalia was completely normal male with a 2.5 cm penile length and bilaterally descendent testes. Ophthalmic examination revealed retinal coloboma and optic disc hypoplasia. Renal agenesis, urethral stenosis and midgut malrotation was detected. Karyotype was 45,X0 without any evidence of mosaicism. SRY gene was positive with polymerase chain reaction. FISH analysis revealed SRY/distal 7q translocation . DNA sequence analysis revealed 16,114,671 mb (142,706,753-158,821,424) deletion from distal part of the 7q, and additional 336,501 kb (154,577,253-154,913,754) deletion from the X chromosome. Two hundred and nineteen gene from 7th chromosom, 6 gene from X chromosome, total 215 gene were deleted.

Conclusions: A few cases of 45 X testicular DSD were published to date. Other clinical manifestations of our patient were compatable with distal 7 q deletion syndrome. Best of our knowledge this is the first case of 45 X testicular DSD with SRY gene rearranged on 7th autosomal chromosome.

P2-d1-1109 Sex Differentiation 3

Turner syndrome: epidemiological study in Tunis

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Background: Turner Syndrome (TS) is often misdiagnosed or diagnosed late which prevents efficient treatment and care. Its epidemiological and clinical characteristics as well as its cytogenetic abnormalities and treatment are unknown in the pediatric population of Tunis.
Objective and hypotheses: To determine epidemiological and clinical characteristics of Turner Syndrome in pediatric departments of Tunis.To individualize most frequent cytogenetic abnormalities and their phenotypic expression.To describe terms and effects of treatments of the growth and gonadal insufficiency.To offer a standardized management in Tunisia for the TS children and a well managed transition to adult care for TS teenagers.
Methods: Retrospective study lead in all the departments of Children Hospital of Tunis over a period of 15 years between January 1997 and September 2012.
Results: Average age at diagnosis was 8years and 9months. Delayed growth was present in 95% of cases. It was the most frequent cause of diagnosis.88% of the girls had delayed puberty and one girl completed spontaneously her puberty. Most frequent dysmorphic signs: hyperthelorism nipples(70%), pterygium colli (45%), fingers brachymetacarpia (35%). Caryotype was made in all the cases and revealed 45,X monosmy in 65% of the cases, one case of mosaicism and one case of structural abnormality without mosaicism. SRY gene has been found in 2 cases. Several malformations were associated: cardiac, renal, hearing,bony, ophtalmic and mental.Screening for autoimmune thyroid disease, diabetes mellitus, dyslipidemia and liver dysfunction was systematically made and was negative. 45,X was associated to the most severe abnormalities.Only 75% of the patients have benefit of GH therapy. None of them befit from undergoing induction of puberty.
Conclusions: First pediatric study of Turner Syndrome in Tunis. Diagnosis is still late. Patterns most be known and management have to be standardized so as to improve the prognosis of this disease.

P2-d1-1110 Sex Differentiation 3

Cardiovascular and renal anomalies in Turner syndrome

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Background: Nephrourologic malformations in Turner syndrome(TS) are frequent, its diagnosis and follow-up is important in order to diminish the morbidity of this disease, Furthermore Cardiovascular diseases account for a threefold higher mortality in women with TS.
Objective and hypotheses: To evaluate the frequency and type of cardiovascular (CV) and renal abnormalities seen in a sample of patients with Turner Syndrome (TS) and to verify the proportion of those anomalies detected.
Methods: Retrospective study of sixty girls with TS aged 2-27 years , the mean age is 14 years, were evaluated. The patients were categorized into 3 groups according to karyotype: group 1 comprised 35 patients with monosomy X (45,X), group 2 comprised 11 girls with mosaicism, and group 3 comprised 14 patients with structural aberrations of X chromosome with or without mosaicism.Data were obtained by personal history of CV and Renal disorders and by results of echocardiogram, Heart MRI; and ultrasonography of the kidneys and collecting system performed after diagnosis.
Results: 26% of patients who underwent echocardiograms presented CV abnormalities versus 44% with heart MRI of the entire study. Among them, bicuspid aortic valve (17%) and aortic coarctation (13%) were the most frequent. Cardiovascular abnormalities are more frequent in patients with monosomy (62%).Renal anomalies were found in 23% of patients who underwent ultrasonography. Among them, horseshoe kidney (36%) and ectopic kidney (22%) were the most frequent, always more frequent with monosomy patients, majority of cases there was no previous knowledge of these anomalies before this evaluation.
Conclusions: The phenotype of TS is highly variable, a cytogenetic evaluation of girls with short stature would allow early diagnosis of a significant number of patients and also early diagnosis and monitoring of associated congenital anomalies. These congenital anomalies seems correlated with severity of loss the X chromosome.

P2-d2-1111 Sex Differentiation 4

A de novo novel heterozygous deletion mutation in steroidogenic factor 1 (SF1, NR5A1) in a 46,XY patient with primary adrenal failure and splenic hypoplasia/aplasia

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Introduction: Steroidogenic factor 1 (SF1, NR5A1) is a nuclear receptor transcription factor that plays a key role in regulating the adrenal, gonadal and splenic development.
Case study: The 6-week-old phenotypic female patient was presented with salt losing adrenal failure early in two days of life. On physical examination, slightly increased skin pigmentation was noted, a pan systolic murmur (grade 3/6) was heard . Hormonal evaluation revealed testosterone 0.91 ng/ml, DHEAS 0.52 µmol/L, P 0.4 ng/ml, 17(OH)P 1.49 ng/ml, Androstenedione 19.1 nmol/L. Karyotype was 46XY. SRY gene was positive. Echocardiography revealed membranous ventricular septal defect. Female gender assignment was made. Treatment was started with oral hydrocortisone, 9α-fluorocortisol and salt supplementation. At 5-month-old, hormonal evaluation revealed FSH 67.54 mIU/mL, LH 4.41 mIU/mL, DHEAS 0.16µmol/L, P 0.2 ng/ml, 17(OH) P 1.86 ng/ml, Androstenedione 4.34 nmol/L. Basal testosterone level(0.21 ng/mL) did not respond after 3-day hCG stimulation(0.22 ng/mL). Pelvic ultrasound scans showed an normal uterus but no ovary . At 10.5-month-old, pelvic MRI revealed normal uterus while ovaries or testis, adrenal grand and spleen were not visualized. Genitography showed the presence of the vagina and uterus with no relationship to the urethra. At laparoscopy, normally developed uterus with fimbriae tubae and ovaries in appearance were found with an atrophic spleen and no adrenal. Splenectomy was performed. Gonad biopsy wasn't taken for some reason. Pathological examination revealed clear spleen underdevelopment. A heterozygous deletion of 143 bps (c.616_758del, p.Gln206LysfsX133) denovo mutated was found to NR5A1 exon 3 which has never been reported.
Conclusions: We identified a de novo novel heterozygous deletion mutation of NR5A1 gene causing 46XY DSD with primary adrenal failure, membranous ventricular septal defect, splenic hypoplasia/aplasia and preserved Müllerian structures and ovary-like gonads.

P2-d2-1112 Sex Differentiation 4

Measurement of ano-genital distance in healthy children at 4 years

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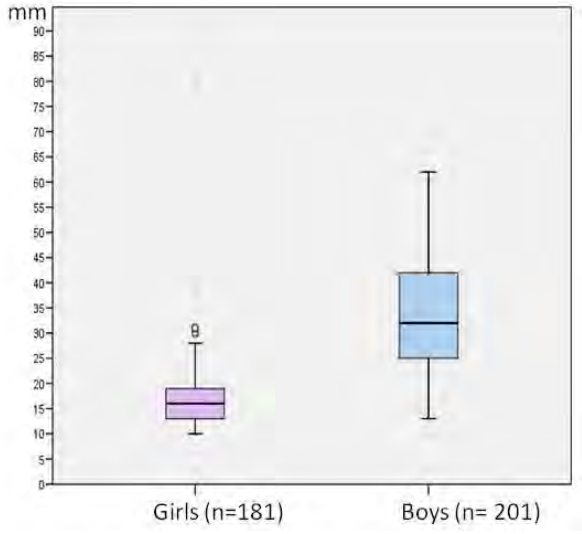
Background: Ano-genital distance (AGD) is a sexually dimorphic anatomic landmark that develops in response to hormone signalling and end-organ response during fetal life.
Objective: To analyze AGD in healthy children at 4 years.
Methods: 482 pregnant mothers recruited between 2004-2007 and their children from a population-based birth cohort study. The research protocol was approved by the Ethics and Research Committee. We analyzed maternal body mass index (BMI), gestational weight gain (GWG), birth weight, BMI at 4 years, Anoscrotal distance (ASD: anus to scrotum) in boys at 4 years and Anofourchetal distance (AFD: anus to fourchette) in girls at 4 years.

Results: 17 mothers were underweight (BMI less than 18,5 kg/m^2), 319 normal (65,8%) (BMI 18,5-24,9 kg/m^2), overweight 108 (22,3 %) (BMI 25-29,9 kg/m^2) and 41 obese (8,5%) (BMI equal or more than 30 kg/m^2). GWG was as recommended in 166 pregnant mothers, low 115 and high 192 (39,6%). Birth weight standardized for 40 weeks was 3372 gr ±397,4 and BMI at 4 years was 16,4 ±1,8 kg/m^2. It was possible to measure AGD in 382 children of the cohort at 4 years, 201 boys and 181 girls. ASD was 33,9 mm ± 11,4 (min 13,0 mm, max 62,0 mm, median 32,0). AFD was 18,3 mm ± 10,6 (min 10,0 mm, max 90,0 mm, median 16,0). Both are represented in figure 1.



[Figure 1. Anogenital distance in girls and boys.]

Conclusions: The sexual dimorphism of AGD in humans evidences that this outcome may respond to in utero exposure to hormonally active agents. Further studies are needed to identify which factors influence.

P2-d2-1113 Sex Differentiation 4

Extreme phenotypic variability of two siblings with 46,XY DSD and a disrupting frame shift mutation in exon 4 of the NR5A1 gene

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Background: The index patient presented shortly after birth as the third child of healthy parents with a short phallus and penoscrotal hypospadias. Androgen insensitivity syndrome was suspected and analysis of the AR gene revealed a short poly glycine repeat of 10 residues in the AR-NTD. Functional assays confirmed a reduced transactivation capacity of the AR and surgical correction of hypospadia was initiated. 12 years later the patient was seen again. A normal pre-pubertal boy with a phallus size of 4 cm, descended testis, normal LH and slightly elevated FSH values. Testosterone and inhibin B values were in the lower normal range. His 15 year old elder sister complained of amenorrhoea. She presented with breast development Tanner B1, a prominent clitoris, highly elevated LH and FSH levels and low testosterone and inhibin B values and a small uterus. Karyotype analysis revealed a normal 46,XY karyotype.
Objective and hypothesis: To unravel the suspected familiar cause of DSD.
Method: Exome sequencing of the family.
Results: Exome sequencing revealed a heterozygous 7bp deletion in exon 4 of the NR5A1 gene in both children and the mother, as well as the shortened poly glycine repeat in the AR. The mutations were confirmed by Sanger sequencing. Despite NR5A1 mutations have been linked to primary ovarian failure, the mother showed no signs of POF and reached menopause at 47 years.
Conclusion: This example shows the high phenotypic range of individuals with even disrupting heterozygous NR5A1 mutations.
The further analysis of exome variants within the family may reveal mutations in modifiers responsible for the variation.

P2-d2-1114 Sex Differentiation 4

Comparison of clinical features between individuals with partial and mixed gonadal dysgenesis

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Background: Partial and mixed gonadal dysgenesis (PGD and MGD) are disorders of sex development which share the same picture of genital ambiguity with either a streak gonad and a dysgenetic testis or two dysgenetic testes. In PGD there is a 46,XY karyotype, whereas in MGD there is a 45,X/46,XY mosaic or its variants.
Objective and hypotheses: The aim of this work was to compare the clinical features of individuals with these conditions, taking into account that in MGD other clinical features associated with the 45,X cell line are expected.
Methods: Our sample comprised 15 individuals with PGD and 15 with MGD. Data obtained from the medical files included maternal and paternal age at birth, birth weight and length, genital and gonadal features, presence of müllerian derivatives and height (in z score).
Results: Paternal age was significantly higher among patients with PGD ($p= 0.044$), and birth weight and length were significantly lower among those with MGD ($p= 0.014$ and $p= 0.001$, respectively), as well as current height ($p< 0.001$). The presence of müllerian derivatives was more frequent among patients with MGD ($p< 0.001$). There were no differences regarding maternal age, position of the urethral meatus, location of the gonads and distribution of gonadal tissues.
Conclusions: Our results indicate that external genitalia and gonadal features of PGD and MGD are indeed indistinguishable; however, the more frequent finding of müllerian derivatives in patients with MGD may indicate a more severe Sertoli cell dysfunction.
As expected, pre- and postnatal growth deficit was more severe in MGD as a consequence of the 45,X cell line.
Finally, higher paternal age in PGD indicates that "de novo" heterozygous mutations may play a prominent part in the etiology of this rare disorder.
This work was supported by Fapesp (2011/50189-7).

P2-d2-1115 Sex Differentiation 4

Stigmatisation of children and adolescents with DSD in medical settings

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Background: Although ongoing controversies about medical management of children with Disorders of Sex Development (DSD) often cite a risk of stigmatization, the evidence rests on scattered case reports rather than systematic study.
Objective: We performed a retrospective study of adults with DSD to document the stigma experienced in diverse settings during childhood and adolescence and to provide material for the development of a screening tool. The current report addresses stigma experiences in medical settings.
Population and method: 63 women with classical congenital adrenal hyperplasia (CAH) of variable severity, mean age 30.5 (range 18-51) years, took part in an 8-10 hour psychological study protocol on the long-term outcome of CAH. The protocol ended with a qualitative interview that covered the patient-perceived impact of CAH and its medical treatment on many aspects of women's lives, focusing on childhood and adolescence. Interviewers were M.A.- or Ph.D.-level clinical psychologists specifically trained for this project. Categorization of stigmatization was based on inductive content analysis of the interview transcripts by two independent raters with a high degree of interrater reliability.
Results: Many women spontaneously reported experiencing genital examinations in childhood and adolescence as adverse stigmatizing events, like being degraded to a study object or target of a freak show, particularly when the examinations included groups of trainees. Some women also experienced as adverse nonverbal and verbal reactions of individual physicians who were unfamiliar with DSD conditions and acted surprised or made other inappropriate comments. Already in childhood some patients began avoiding medical exams.

Conclusions: Genital examinations constitute salient events for patients with DSD. They are easily experienced as strongly stigmatizing, especially when combined with teaching, and worst if the teaching involves groups of trainees.

P2-d2-1116 Sex Differentiation 4

Clinical and hormonal variations associated with androgen receptor gene mutation

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Introduction: The molecular heterogenity of androgen insensitivity syndrome (AIS) leads to a wide range of clinical spectrum and the same mutation is associated with different phenotypes. The differential diagnoses can be difficult in AIS from 5-alpha-reductase deficiency (5aSRD), partial gonadal dysgenesis, timing defects. Testesterone to dihidrotestesterone ratio (T/D) is not always helpful in differential diagnoses and genetic analysis may be needed for definitive diagnoses.

Case study: Androgen receptor (AR) gene analysis of 23 patients, whom had 46,XY disorders of sex development with normal testesterone synthesis and did not demonstrate 5aSR gene mutation were evaluated. AR gene mutation is identified 5 of 23 (%21,7) cases. Case 1: A novel mutation (p.val30met) in exon 1 of *AR gene* was identified in a patient with clinical features of CAIS and a history of umbilical hernia operation at 3 months old. This was a case with a high T/DHT ratio suspicious for 5aSRD.

Case 2: In a male raised 2.8 years old case (Sinnecker 3) with a high T/DHT ratio (17.5), Gly712glu homozygot mutation in exon 4 of *AR gene* was identified.

Case 3 and 4: The mutations in 10,4 and 12,2 years old patients with unambiguous females were p.gly689X and p.D691E in exon 4 of *AR gen*, respectively.

Case 5: A 3,27 years old patient with clinical sign of PAIS, two different silent mutations that does not lead amino acid changes were identified (exon1 and exon7) in *AR gene*.

Conclusion: Patients with *AR gene* mutations can admit with a variety of clinical and hormonal findings and hormone results are not helpful all time. Although genetical analysis are not widely available, AIS especially partial forms are complex to decipher. Advances in genetic have made then diagnosis easier and quite rapid.

P2-d2-1117 Sex Differentiation 4

The role of anti-Mullerian and inhibin B hormones in the elevation of 46 XY disorders of sex development

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Background: Disorder of sex development are congential conditions in which development of chromosomal, gonadal, or anatomic sex is atypical.

Objective: To assess the sensitivity and specificity of the baseline anti-Mullerian hormone (AMH) and inhibin B measurements in the diagnostic workup of infants, children and adolescents with different subtypes 46 XY disorders of sex development (DSD).

Patients and methods: Study was conducted on 43 patients diagnosed as 46 XY DSD children and adolescents comparing them with 43 healthy male age matched control group in The New Pediatric Hospital, Cairo University. The mean age of the studied cases was 5.16 ± 4.24 years. All of the patients had undergone karyotyping, blood samples in the form of testosterone, dihydrotestosterone (DHT) and ▲4 androstendione (▲4A) basal and after HCG test. Basal dehydroepiandrosterone (DHEA) also had been measured; ultrasonograghy and some cases underwent the laparoscopy or gonadal biopsies. Basal AMH & inhibin B had been measured in both cases and controls.

Results: There were significant correlations between basal AMH and HCG stimulated testosterone and DHT ($r = 0.64$; $p < 0.001$ and $r = 0.52$; $p < 0.001$ respectively). Also, a positive significant correlations were found between inhibin B and HCG stimulated testosterone and DHT ($r = 0.62$; $p < 0.001$ and $r = 0.44$; $p = 0.003$ respectively). A highly significant Correlation was found between AMH and inhibin B ($r = 0.78$; $p < 0.001$). The sensitivity of AMH was (96.6%), specificity (60.7%), NPV (89.5%) PPV (83.6%).The sensitivity of inhibin B was (96.6%), specificity (67.9%), NPV (90.5%) PPV (86.2%), best cut-off value was (41.9 IU/ml) and AUC of ROC curve was= 0.81, ($p< 0.001$) with overall accuracy was (87%).

Conclusion: Both AMH and inhibin B are valuable reliable non invasive parameters for the detection of functioning testicular tissues in prepubertal patients.

P2-d2-1118 Sex Differentiation 4

Disorders of gonadal differentiation: histological evaluation, gender assignment and surgical approach

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Objective: To determine the choice of gender assignment and surgical approach in patients with different morphological variants of gonadal disgenesis (GD).

Methods: The appearance of genitalia, karyotype, ultrasound and laparoscopy, serum LH, FSH and testosterone were examined in 25 patients from 0 to 1,5 y.o. with GD.

Results: All patients had ambiguous genitalia, urogenital sinus, uterus. Scrotal testicle on one side was found in 12, gonads were not palpable in 13. Karyotype was mosaic in 7 children; 46, XY - in 18. Hormonal tests showed high FSH in 40% prepubertal patients and low testosterone after gonadotropin stimulation in 36%. As the result of clinic and histology there were 4 morphological variants. The mixed GD was established in 6 (24%) patients, complete GD - in 2 (8%), partial GD - in 14 (56%). The male gender was assigned in all patients with mixed GD and in 8 with partial GD. All patients with complete GD, and 6 with partial GD were brought up as females. Unilateral laparoscopic gonadectomy was performed in 14 patients, bilateral - in 8. Ovotesticular DSD was revealed in 3 (12%). All of them were evaluated as female. Mixed gonads consisted of 2 or 3 compartments separated by connective constriction. Histology showed disgenetic testicular tissue and mature ovarian tissue with primordial follicle in only 2. These patients underwent separation of gonads with excision of all testicular tissue. Ovarian segments were preserved in bilateral gonads. In other case we found disgenetic testis and immature stroma of ovary. This patient underwent gonadectomy.

Conclusions: Gender assignment and surgical approach in patients with disorders of gonadal differentiation was based on the morphological study defining the phenotype and potential of puberty.

P2-d2-1119 Sex Differentiation 4

Persistent Müllerian duct syndrome: a novel mutation in anti-Müllerian hormone gene

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Introduction: Persistent Müllerian Duct Syndrome (PMDS) is characterized by failure of regression of the müllerian ducts in males, leading to the presence of uterus, fallopian tubes and the upper part of the vagina in 46XY, phenotypically male patients. This is usually caused by mutations of the anti-Müllerian hormone (AMH) or AMH type 2 receptor gene.

Case study: A greek male infant, aged 2 months, baby of a dizygotic twin pregnancy, born to apparently healthy and non consanguineous parents, underwent surgery for the repair of left inguinal hernia. Right cryptorchidism and left ureteropelvic junction stenosis was diagnosed as well. The patient's paternal grandfather and great grandfather were both reported to have both testes at the left side of the scrotum. During surgery it was found that both

testes were at the left side in the scrotum and a morphoma like uterus between them. The endocrine blood investigations, including thyroid function test, LH, FSH and sex steroids levels were normal. AMH levels were undetectable in serum. The genetic studies showed that the patient is a compound heterozygous for two mutations of the AMH gene. The first one, detected once more in a patient from Kosovo, is a large 23bp duplication of bases 2339-2361 in the 5th exon, leading to the incorporation of 3 wrong amino-acids before a Stop codon, and deleting all the C-terminal bioactive fragment of AMH. The second one is a T to G transversion at position 1113 in the second exon, leading to a Valine to Glycine change at amino-acid position 174. This is a mutation detected for the first time to our knowledge.Unfortunately, no blood sample for DNA analysis from the grandfather and the great grandfather was available.
Conclusion: The diagnosis of PMDS in patients with cryptorchidism associated with inguinal hernia requires a high index of suspicion, in order to prevent complications such as malignancy. Genetic counseling to the family of affected patients is also necessary.

P2-d2-1120 Sex Differentiation 4

Mutation analysis for androgen receptor gene in patients with suspected androgen insensitivity syndrome

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Background: Androgen insensitivity syndrome (AIS) is a rare disease due to end organ resistance of androgens. AIS is commonly caused by the mutations of androgen receptor (*AR*) gene located on chromosome Xq11-12. The mode of inheritance is hemizygous, where males get severely affected and females remain as carriers.
Objective and hypotheses: We present mutation of *AR* gene in 10 patients with clinically suspected AIS.
Methods: Patients with 46, XY karyotype and sexual ambiguity with or without gynecomastia attending the Endocrine clinics, AIIMS, New Delhi were enrolled for the study.A detailed clinical examination was done in all of them. The study was approved by AIIMS Ethics committee. The genotype of the patients was analysed for *AR* gene mutations. PCR amplification was carried out using 11 pairs of primers for 8 exons and the flanking region of *AR* gene.
Results: Twenty two patients were suspected to have AIS. Seven out of 22 cases are being reared as females. Three patients had female like external genitalia and had sought medical attention for primary amenorrhoea. Four out of 7 cases had moderate to severe clitoromegaly. Out of these molecular analysis of AR gene was carried out in 10 cases. Detailed in table.

S.No. R 17	Age at evaluation (yrs) 4	Sex of rearing male	mutation A ins exon 8, p878 fs.	External genitalia Scrotal **hypospadias, bifid scrotum,** testes in inguinal region
R 38	19	male	A ins exon 2, p 560 fs.	microphallus, testes in labioscrotal folds.
R 64	18	male	Y p.594 F, GCAGCAGCA del , (exon 1)	Microphallus, perineal hypospadias, testes in scrotum.
R 8	28	male	E p.772 A	Microphallus, perineal hypospadias, Lt testes inguinal canal Rt testes in scrotum.
R 15	7	male	Del A (exon5), P 728 fs.	Microphallus, perineoscrotal hypospadias. Testes in scrotum
R 42	2	male	Del A (exon5), P 728 fs.	Perineoscrotal hypospadias, Rt testes not identified, lt testes in inguinal canal.
R 11	23	female	D p.865 N	Gonadectomy done, Female genitalia.
R 29	18	female	T p.105 R	Gonadectomy done, Bifid scrotum,
R 16	16	male	P p.133A & GCAGCAGCA del , (exon 1)	testes in pelvic cavity, Penoscrotal hypospadias, microphallus.
R 60	14	male	GCA del, fs p.79 onwards	Testes in labio scrotal folds, microphallus.

[Mutation and phenotype of patients with AIS]

Conclusions: Mutations were observed in AR gene in all 10 cases. Two of these mutations (D865N and E 772A) have been reported earlier in two cases from Europe and Canada.

P2-d2-1121 Sex Differentiation 4

A case of SOX 9 mutation without campomelic or acampomelic dysplasia

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Background: The bipotential gonads in embryos can differentiate in either testes or ovaries. Testicular differentiation and development of male genitalia needs the presence of the SRY gene. The differentiation of bipotential cells in Sertoli cells needs the SRY action via the SOX 9 gene. SOX 9 mutation causes, dependent on the location, campomelic or acampomelic dysplasia with or without disorder of sexual development. Until now, only two XY patients with sex reversal due to SOX 9 mutation without bone anomalies have been described.
Case vignette: We are reporting a 15-year-old patient of normal female phenotype with absent breast developement and primary amenorrhea. Stage of puberty was Tanner B1, PH 3. Laboratory examination showed normal LH but high FSH, and low estradiol. Consequently, karyotyping was performed, which revealed 46 XY. These findings, combined with low AMH and low testosterone suggested gonadal dysgenesis. A human chorionic gonadotropin (hCG) test was performed, which showed no adequate response (testosterone after stimulation 0,2 µg/l, reference range >9µg/l). Genetic examination revealed an existing SRY gene, but a heterozygous deletion about 483kbp upstream of SOX9 was identified as cause of the sex reversal. MRI of the pelvis showed a normal uterus and a gonad on the left side. Laparoscopy and bilateral gonadectomy was performed and revealed a streak gonad on the right side and a gonadal tumor on the left side, identified as dysgerminoma by histopathological work-up.
There was no evidence of any bone or craniofacial abnormalities either in the patient or in her parents. All radiographic findings (including CT of the thorax) were normal.
Conclusions: Absence of bone anomalies in 46 XY DSD does not exclude mutations in the SOX 9 gene.

P2-d2-1122 Sex Differentiation 4

Effective treatment with low dose dihydrotestosterone gel on three Chinese boys with 5-alpha-reductase II deficiency

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Background: 5-alpha-reductase II deficiency is a rare autosomal recessive form of 46, XY disorder of sexual differentiation. This is caused by mutation in steroid 5-alpha-reductase type 2 gene (SRD5A2). Dihydrotestosterone (DHT), which is available in the form of a topical gel, is theoretically effective in promoting virilization in this group of patients. Most published reports in the literature used relatively high dose of DHT gel, which resulted in virilization, but also side effects of accelerated growth, bone age advancement and growth of pubic hair. There are only limited data on the clinical response and circulating DHT levels following topical application of low dose DHT gel in this condition.
Case report: Three Chinese boys were diagnosed to have 5-alpha-reductase II deficiency by urinary steroid profiles. They had variable degrees of virilization (two had micropenis and one had ambiguous genitalia and was mistaken as a girl initially). They were all treated with low dose dihydrotestosterone gel at 0.2-0.5mg/kg/day topically at the suprapubic area at the age of 8 to 30 months. Circulating DHT levels were monitored every 4 to 6 hourly after the application of DHT gel. All of them had good response to treatment after DHT gel application for 8-12 months with increased phallic length from 1.9±0.12cm to 3.1±0.12cm, and phallic width from 0.93±0.12cm to 1.2±0.2cm. None of them suffered side effects namely accelerated growth, bone age advancement and growth of pubic hair. Peak circulating DHT levels

were attained at 4 to 6 hours after topical application at 35-60ng/dL.
Conclusions: Low dose DHT gel is useful in children with 5-alpha reductase II deficiency in promoting phallic growth with no side effects observed in our patients.

P2-d3-1123 Sex Differentiation 5

Pubertal virilization of 46,XY female adolescent without adrenal insufficiency due to a novel heterozygous mutation in steroidogenic factor-1

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Introduction: Steroidogenic factor-1 (SF-1) gene mutations cause disorders of sexual development due to gonadal dysgenesis, particularly in 46,XY individuals. In cases exhibiting this mutation, the phenotype is heterogeneous, and it may vary within a spectrum ranging from complete female appearance to an infertile male. Virilization observed in some cases in the pubertal age group may lead to diagnostic difficulties.
Case study: The patient, who was raised as a girl, presented at our clinic for the first time at the age of 10.14 years, and It was found out that virilization of the external genitalia was noticed within the past year. Cliteromegalia and pubic hairs were noticed. The Sinnecker scoring was determined to be consistent with stage 2. In the laboratory evaluation, serum LH level was 8.39 mIU/mL, FSH was 44.4 mIU/mL, total testosterone was 181.4 ng/mL. The karyotype was 46,XY. There is no adrenal pathology. The laparoscopic investigation revealed that atrophic gonads and the remnant of the fallopian tube at pelvic localisation. Pathological evaluation showed atrophic testis and Sertoli-cell-only pattern in the biopsy samples. No germ cell and Leydig cell were encounterd. At psychiatric evaluation, her sexual identity characteristics were consistent with the female sex. DNA analysis showed heterozygote c.1308-1314 del7bp frameshift mutation. The mutation encountered in our case is a novel heterozygous mutation, which has not been reported before. Patient raised as girl and gonadectomy has been performed.
Conclusions: Even though testis structure exhibits distinct dysgenesis and the number of Leydig cells in the gonads is very scarce in 46,XY DSD cases with SF-1 gene mutations, born with a female phenotype and raised as a girl, they still can promote sufficient androgen synthesis to cause pubertal virilization. In cases with SF-1 mutations, which can also cause dysgenetic gonad development, the cause of development of pubertal virilization remains unclear.

P2-d3-1124 Sex Differentiation 5

SRD5A2 gene mutation can lead to sex development disorder; a case of a Turkish patient with 46,XY

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Background: 5-alpha-reductase type 2 deficiency (264600) is one of the rare development anomalies. Affected 46,XY individuals usually present with ambiguous genitalia characterized by pseudovagina, microphallus, cryptorchidism and perineoscrotal hypospadias, at birth and are often raised as females. The abnormal 5-alpha-reductase type 2 as a result of mutations in the *SRD5A2* gene could lead to 46,XY disorders of sex development. Therefore, genetic testing of *SRD5A2* is a useful tool for the definitive diagnosis of 5-alpha-reductase type 2 deficiency. In this study, we report a novel mutation in *SRD5A2* gene in a Turkish patient with 5-alpha-reductase type 2 deficiency.
Methods: Five coding regions of *SRD5A2*, including exonic- intronic boundaries, were amplified by using spesific primers, and sequenced directly after amplification.
Results: Two heterozygous mutations, c.164T>A that leads to a amino acid substitution p.Leu55Gln and c.269A>C, leading to a amino acid substitution p.His90Pro were detected in the examined patient. The latter one, c.269A>C, was a novel mutation found in the patient.
Conclusions: It is important to determine the genetic factor leading to 5-alpha-reductase type 2 deficiency in patients for the proper treatment. In this report, we detected a novel mutation which can cause to development disorder, but in order to have a proper understanding about the mutation effect, functional analysis should be carried.

P2-d3-1125 Sex Differentiation 5

A case of disorder of sex development (DSD) that showed bilateral testicular development with extremely low population of a 46,XY lineage

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Case presentation: The patient was born at 37 weeks of gestational age with 2248g of birth weight, and the external genitalia showed micropenis, cryptorchidism and hypospadias. The patient was conceived through IVF using a sperm donor due to azoospermina of the patient's father. The right and left testes was in sac and in the inguinal canal, respectively. We could not find any organs derived from Müllerian ducts. We selected female as rearing sex. She showed mild intellectual disability and Turner's signs including webbed neck and short stature less than -3SD. Cytological analysis using peripheral lymphocytes suggested the karyotype was 45XO, and we could not detect the Y chromosome even by fluorescence in situ hybridization (FISH) using 500-cell analysis. Whereas *SRY* and *DYZ* were detected by PCR from peripheral lymphocytes, suggesting that the patient had the 46 XY lineage, however, its population was extremely low. Human chorionic gonadotropin (hCG) test revealed that the gonads had testicular function. From both gonads, Sertoli cells and immature Leydig cells were identified, and any ovarian tissue or cells were not observed.
The patient showed atypical ABO blood type, A_1B_3, that agglutinated to anti-A antibody normally and weakly to anti-B antibody.
Discussion: The cytological analysis and the PCR data suggested the patient had 45,X/46,XY, however, comparing to typical mixed gonadal dysgenesis (MGD), the present case was exceptional, because despite of the extremely low population of the 46XY lineage, both gonads were developed as testes. Additionally, the patient revealed to have the atypical ABO blood type. In order to elucidate the etiology genetically, especially considering the possibilities of chimerism, we performed microsatellite analysis of the patient and her mother DNA samples.
However, it resulted in unsuccessful mainly because of un-availability of father's DNA sample.

P2-d3-1126 Sex Differentiation 5

A novel mutation of the aromatase gene (CYP19A1) in 46,XX two siblings cases of assigned with different gender

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Background: Aromatase deficiency is a rare cause of 46, XX disorders of sex development (DSD).
Methods: We report two siblings assigned to different gender with 46, XX genotype.
Case 1: 14 years old adolescent assigned to male gender, admitted to our hospital for operative corrections of hypospadias present since birth. The parents

were non-consanguineous from the same village. According to the assigned gender height 154.9 cm (SDS: - 2.5), weight: 57 kg (SDS: -0,6), fallus 2 cm, gonads were non-palpable, Prader stage: 3. In his laboratory findings; bone age was 11 years, FSH: 70 mIU/l, LH: 30 mIU/l, free testosteron:0,9 pg/ml, E2:22,9 ng/ml. ACTH, cortisol, 17 OHP were normal. Karyotype was 46,XX, FISH: SRY (-). Ultrasonography (USG) revealed a right over 19x14 mm and a left over 15x12 mm. In the laparoscopy there was bilaterally normal overs and a small uterus. Biopsy of the right gonad was consistent with ovary. Molecular analysis of aromatase gene (CYP19A1) revealed the presence of a novel homozygous missense mutation (R115T).

Case 2: A 8 years old child assigned to female gender the sister of case 1 admitted to our hospital. Her height was 125.5 cm (SDS: -0,3), weight was 22.3 kg (SDS: -0,9), fallus 1 cm (Prader stage 2). In her laboratory findings bone age was, 5 years, FSH, LH were high and ACTH, cortisol, 17 OHP were normal. Karyotype was 46, XX. USG revealed a right over 12x11 mm and a left over 13x 10 mm. Same homozygous mutation was found in CYP19A1 gene in this patient. Their parents were heterozygote for the same mutation. Interestingly, during both of the pregnancies the mother did not develop any signs of virilization.

Conclusion: In virilised 46, XX patients after congenital adrenal hyperplasia is ruled out aromatase deficiency should be considered without any virilization in the mother during pregnancy. An early diagnosis is essential for sufficient management of the affected cases.

P2-d3-1127 Sex Differentiation 5

Disorders of sex development: a review of 139 cases

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Background: Disorders of sex development (DSD) is defined as any congenital conditions in which chromosomal, gonadal or anatomical sex is atypical.
Objective: The aim of this study is to analyze the epidemiological, clinical, biological and genetic DSD Children's and to share experiences concerning these rare groups of patients across centres regarding diagnostics as well as management and care.
Methods: This is retrospective study between January 2003 and March 2013 for DSD patients with discordance between genotype and phenotype with the problem of sexual identity or gender statement. We excluded cases of isolated micropenis and hypospadis; these cases are conducted from the unit of pediatric endocrinology of Children's Hospital in Casablanca.
Results: 139 cases of DSD were retained, 75 cases had a 46 XX karyotype, 53 cases had a 46 XY karyotype, and 11 cases had an anomaly of the gonosomes. On 46, XX DSD, the most frequent reports involve cases with 21-α-hydroxylase deficiency congenital adrenal hyperplasia in 58cases, 11 βhydroxylase in 3cases, and POR deficiency in 1case.A final diagnosis on the other hand could be established only at 28 cases for 46, XY DSD of our series: Disorder of androgen action with complete androgens insensitivity syndrome: 6cases and partial androgens insensitivity syndrome: 5cases. Disorder of androgen synthesis, by the case of 5 alpha-reductase deficiency: 5cases, StaR: 1case, 3β-HSD: 1case and 17 βHSD: 1case. Disorder of gonadal development: by complete gonadal dysgenesis: 1case and partial gonadal dysgenesis: 3cases. Ovotesticular DSD holds a considerable part of our series, since it was found at 3 cases 46, XX and 5 subjects 46, XY. For 35 patients, the etiologic is still in progress.
Conclusions: The management of patients with DSD, including decisions about sex of rearing, must be carried out by a specialized team and include an extended genetic investigation as well as psychological considerations in addition to the DSD diagnosis.

P2-d3-1128 Sex Differentiation 5

Patients with 45X/46XY lie within the broad spectrum of Turner syndrome: experience from one clinical center

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Background: 45,X/46,XY DSD have been sometimes discussed as being a variant of Turner syndrome (TS). Nevertheless the presence of Y chromosome in tissue organ systems may modify many aspects of the presentation, risks, needs, and management relative to that of TS girls.
Objective and methods: The aim of the study was to describe the phenotype of the X/XY syndrome by studying the clinical characteristics of 10 children with this type of karyotype who were managed at single institution between 1997 and 2012.
Results: The mean age of diagnosis was 6.44 yrs (SD 5.3 yrs; median: 6.81 yrs; range 0.0-13.3 yrs). 6/10 were reared as female (F) and diagnosed as TS, 4/10 were reared as male (M). In 9/10 cases postnatal diagnosis was made: in 5 because of short stature and other features of TS, in 4 because of ambiguous genitalia. There was one F diagnosed prenatally. Corrective surgeries were needed in 4 DSD patients (M), gonadectomy was performed in all 45,X/46,XY children with TS (F). Cardiac anomalies and horseshoe kidney were found in 5/10 (3F, 2M) and 2/10 (1F,1M), respectively. Short stature (hSDS < -2.0) was present in 9/10 patients, however only TS were treated with growth hormone.
Conclusions: Regardless the phenotype of external genitalia and the decision as to the gender's register all children with 45,X/46,XY require clinical evaluation similar to that performed in TS patients. All patients with DSD 45,X/46,XY and short stature should be recognized as potential candidates for growth hormone therapy.

P2-d3-1129 Sex Differentiation 5

Bilateral inguinal haernia in a 3-week-old girl: an unusual presentation of XY-DSD caused by 17α-hydroxylase/17,20-lyase deficiency and practical recommendations for diagnostic workup

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Background: 17α-hydroxylase/17,20-lyase Deficiency is a rare type of congenital adrenal hyperplasia causing decreased production of cortisol and sex steroids and increased synthesis of mineralocorticoid precursors due to a defect of the CYP17A1 gene that encodes the P450c17 enzyme. This enzyme has 17α-hydroxylase and 17,20-lyase activity. The former is essential for cortisol synthesis and the latter catalyses C21- conversion to C19-Steroids yielding mainly DHEA for further sex-steroid synthesis.
Methods: We report on a case of a 3-week-old girl from a non consanguineous couple with suspicion bilateral inguinal hernia admitted for ultrasound to our clinic. Pregnancy was achieved by intracytoplasmic sperm injection (ICSI). Genitalia looked normal. The ultrasound examination revealed testicle-like structures in both labia majora. Laboratory tests repeatedly showed low cortisol with normal sodium and potassium levels. ACTH was 34,3 pg/ml (10-130 pg/ml). Normal values for FSH, LH and estradiol were obtained. Karyotyping showed a 46,XY genotype.
While we first suspected androgen insensitivity syndrome the eye-catching low cortisol levels lead us to consider rare types of congenital adrenal hyperplasia. Gas chromatography-mass spectrometry (GC-MS) urinary steroid analysis showed a steroid profile dominated by corticosterone metabolites and a complete lack of cortisol metabolites and androgen metabolites reflecting complete absence of 17α-hydroxylase and 17,20-lyase activity. After start of hydrocortisone treatment mineralocorticoid precursor synthesis declined significantly.
Conclusions: Suspicion of bilateral inguinal hernia warrants thorough diagnostic work up. Urinary steroid profiling with gas chromatography-mass spectrometry (GC-MS) is an invaluable tool in detecting rare disorders of

steroid biosynthesis. The procedure being non invasive, enabled final diagnosis of this rare steroid enzyme deficiency in one of the youngest patients ever reported.

P2-d3-1130 Sex Differentiation 5

Adolescent with Frasier syndrome - WT1 mutation as a cause of 46, XY DSD and progressive nephropathy

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Introduction: Frasier syndrome (FS) is a rare disorder defined by 46 XY disorder of sex development and progressive glomerulopathy. Patients present normal female external genitalia, streak gonads, XY karyotype, and frequently develop gonadoblastoma. Glomerular symptoms consist of childhood proteinuria and nephrotic syndrome characterized by nonspecific focal and segmental glomerular sclerosis, progressing to end-stage renal failure in adolescence or early adulthood.
Case report: Seventeen year old adolescent was raised accordingly to female gender. At the age 15, she complained of persistent headache and was detected hypertension (202/137mmHg) in the physical examination. During the study of the hypertension was diagnosed acute kidney failure, nephrotic proteinuria, dyslipidemia and hypertensive retinopathy. The renal ultrasound (US) showed normal kidney size with a hyperechoic cortex. The renal biopsy showed diffuse mesangial sclerosis and started treatment with enalapril, losartan, nifedipina and alfacalcidol. She also had primary amenorrhea and absence of thelarche. The endocrinology study revealed, 46 XY karyotype and a hypergonadotropic hypogonadism. The pelvic US showed infant uterus and streak gonads, so she performed bilateral gonadectomy and the histological study revealed the presence of bilateral gonadoblastoma. Started estrogens therapy with good results, but she suffered a progressive deterioration of kidney function and now she has a chronic kidney failure. Because of the imminent risk of kidney tumour, she performs regularly renal US. The genetic study confirmed the mutation in intron 9 of the WT1 gene.
Conclusion: The patients with FS have higher risk of gonadal tumor, so elective bilateral gonadectomy is indicated. Since the great majority of FS patients have normal female external genitalia, sex reversal is not suspected before they present delayed puberty. Therefore, molecular screening of WT1 gene is very important to confirm the FS diagnosis.

P2-d3-1131 Sex Differentiation 5

A rare case of siblings with partial androgen insensitivity syndrome diagnosed following gynaecomastia and the successful management of gynaecomastia using tamoxifen

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Background: Almost all patients with partial androgen insensitivity syndrome (PAIS) develop gynecomastia (GM) during puberty. However, PAIS is rarely diagnosed following GM during puberty.
Case reports: Two siblings (13- and 16-year-old boys) were referred to our department for evaluation of GM at pubertal period.
Results: Physical examination revealed Tanner stage 3 breast development and pubic hair with a female-like distribution. No virilization disorders were noted. The laboratory data showed that the karyotype of both patients was 46, XY, testosterone synthesis was increased, and LH levels were within the normal range. The laboratory findings were consistent with PAIS. Genetic analysis revealed a hemizygous mutation at position Arg789Ser of the androgen receptor (AR) gene, which has been previously reported to be associated with PAIS. Our patients exhibited a remarkable reduction in the severity of GM after treatment with tamoxifen as an antiestrogen therapy without side effects.
Conclusion: PAIS should be considered in subjects with pubertal gynecomastia, even if the subjects do not exhibit a virilization disorder. Recent studies have reported that tamoxifen may be effective in reducing persistent pubertal GM, although no previous reports have described the administration of tamoxifen to treat GM in cases with PAIS. We suggest that tamoxifen could be beneficial for treating GM in cases with PAIS.

P2-d3-1132 Sex Differentiation 5

Analysis of 5α-reductase type 2 and androgen receptor gene in Korean patients with ambiguous genitalia

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Purpose: Normal penile development is dependent on testosterone, its conversion via steroid 5α-reductase type 2, to dihydrotestosterone, and a functional androgen receptor. Mutations in the 5α-Reductase type 2 (SRD5A2) or androgen receptor (AR) gene impair masculinization and may be associated with ambiguous genitalia. In order to explore these possibilities and to make definite diagnosis, we planned this gene study.
Methods: In this study, we examined the SRD5A2 and AR genes in 15 Korean patients with ambiguous genitalia including micropenis and hypospadia (age, 8 months-18 years; median, 2 years), together with 80 control males. We applied polymerase chain reaction and direct sequencing to analyze the coding regions of SRD5A2 and AR genes.
Results: We identified one novel pathogenic mutation of SRD5A2 gene in 4 year old patient with ambiguous genitalia. He manifested 1-1.5 cm length of micropenis, hypospadia and bifid scrotum. The result of hCG stimulation test was negative. The G>C transition was located at the position 214 of exon 1 (371 bp). There were no mutations of SRD5A2 and AR gene in other 14 patients and 80 control males.
Conclusion: Mutations in SRD5A2 seem to be associated with ambiguous genitalia. Gene study can be important role for the definite diagnosis and further treatment of micropenis, hypospadia or other ambiguous genitalia.

P2-d3-1133 Sex Differentiation 5

Absent visualization of a hypoplastic uterus in a 16-year-old with complete 46,XY gonadal dysgenesis (Swyer syndrome)

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Background: A 16-year-old female presented with primary amenorrhea, absent breast development, Tanner V pubic hair, sparse axillary hair and female appearing external genitalia. Karyotype revealed: 46 XY with detectable SRY, elevated FSH and LH hormones, testosterone and androstenedione in the female range, normal dehydrotestosterone. Estrogen, estrone and ultra sensitive estradiol were in the prepubertal range. HCG stimulation did not result in an increase in testosterone levels, and the inhibin B level was undetectable; suggesting absent testicular function. Anti-Mullerian hormone level was < 0.1. On trans-abdominal pelvic ultrasound, no ovaries, uterus or gonads were visualized. After the initiation of hormonal replacement therapy, MRI of the pelvis revealed a hypoplastic uterus and no definitive ovaries. After laparoscopic bilateral gonadectomy the pathology report showed some Fallopian tissue on the left gonad with cystic changes. On the right gonad there was some ovarian stromal tissue without follicles. There was no evidence of gonadoblastoma.
Objective and hypotheses: To report an uncommon presentation of an adolescent female with 46 XY complete gonadal dysgenesis.
Design: Case report.
Methods: *Setting:* Pediatric Endocrinology Clinic. *Intervention(s)*: Pelvic US, Pelvic MRI, cystoscopy, vaginoscopy, exploratory laparoscopy.
Results: The patient had 46 XY complete gonadal dysgenesis with a hypoplastic uterus that was not initially visualized on pelvic US. 6 months after

initiation of estrogen therapy, her uterus was visible on MRI, and menarche occurred.
Conclusions: Swyer syndrome with XY complete gonadal dysgenesis may present with absent genitalia and an "absent" uterus on pelvic ultrasound. However, a uterus is in fact present and may be visualized on MRI, particularly after treatment with estrogen. Corrected diagnosis is important due to reported increase of gonadoblastoma. Option of pregnancy is available.

P2-d3-1134 Sex Differentiation 5

Penile agenesis: case report and management in a limited resources country

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Background: Penile agenesis (PA) is an extremely rare anomaly with profound urological and psychological consequences. Female gender has been assigned to 46,XY newborns affected by aphallia, possibly resulting in subsequent gender dysphoria. Prenatal and postnatal effects of the androgens on the brain and sexual orientation cannot be modified later. Therefore, patients affected by aphallia should be raised as males. Because definitive forearm flap phalloplasty is generally not recommended before puberty
Case presentation: We reported the case of a 5 months old genotypic male (46 XY) infant. On examination the patient had an absent penis, with a normal looking scrotum and bilaterally descended testes. Anus was normally placed and the urethral opening was visible on the perineum in midline. Patient did not have dysmorphic features or clinical evidence of any other associated anomaly. Ultrasound examination revealed normal looking kidneys and urinary bladder with absence of corpora cavernosa and corpora spongiosum. because of the local cultural specificity and the limited ressources, the child is raised as a boy in expectation of a phalloplasty surgery.
Conclusion: Opposite gender should not be assigned in patients affected by penile agenesis, who are better raised according to their karyotype and hormonal production. Definitive phalloplasty in adults may achieve good results. Nevertheless, this procedure is generally performed in postpubertal boys and it is not easily available in limited ressources countries. Therefore, the social and psychological concerns justified this type of phalloplasty as a palliative preliminary procedure. In those countries where definitive forearm phalloplasty is not available this method may also be justified in older children as an attempt at a definitive procedure.

P2-d1-1135 Thyroid 4

Predictors for thyroid carcinoma in Israel: a national cohort of 1,624,310 adolescents followed for up to 40 years

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Introduction: Data on adolescent predictors of thyroid cancer in adulthood are scant**.**
Objective: To find predictors in adolescence for thyroid cancer in adulthood.
Methods: In order to evaluate potential risk factors for thyroid cancer we linked two national data sources: the military recruitment health examinations and the Israel National Cancer Register. The study population (N=1,624,310 participants) included 1,145,865 Jewish males, aged 16-19 when examined between 1967 and 2005, and 478,445 Jewish females aged 16-19 when examined between 1989 and 2005. The cancer follow-up extended up to 2006. Multivariable Cox proportional hazards modeling was used.
Results: During 24,389,502 person years of follow-up 760 incidence cases of thyroid cancer were identified. The mean age at diagnosis was 25.2±4.2 years for women and 37.2±10.0 years for men**.** Women had a substantially higher incidence [birth cohort-adjusted hazard ratio (HR)=5.70 (95% CI 4.45- 7.31), $p< 0.001$)]. Height predicted incidence in both sexes, with birth cohort-adjusted HRs of 1.03 ($p< 0.001$) in males and 1.04 ($p< 0.001$) in females, per 1 cm increment in height. In males, but not in females, there was a graded association between education, as measured by years of schooling, and incidence of thyroid cancer. BMI was not associated with incidence. In a multivariable analysis of 617,613 males and 469,185 females examined from 1989 onwards, which included sex, birth year, height, and education, the excess risk in females persisted strongly (HR= 5.54, 95% CI 4.30-7.13), as did the association with height.
Conclusions: Female sex, measured height in adolescence, and later birth cohorts were independent predictors of thyroid cancer in adults in Israel. Further study is needed to unravel the mechanisms whereby height is associated with thyroid cancer.

P2-d1-1136 Thyroid 4

Congenital central hypothyroidism associated to multiple pituitary hormone deficiency has an impaired thyroid function similar to congenital primary hypothyroidism due to ectopic or eutopic thyroid

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Background: Congenital central hypothyroidism (CCH) is mainly associated to congenital multiple pituitary hormone deficiencies (CMPHD). Although this is a life-threatening disorder, due to its low frequency, most of worldwide neonatal screening programs by means of TSH determination do not diagnose this disease.
Objective and hypotheses: In the present study we analyzed the severity of CCH in patients with CMPHD and compared them with a large cohort of patients with primary hypothyroidism detected with a neonatal screening program.
Methods: Thirty three patients, Group A, (24 males) with CMPHD were included in the present study and compared with a cohort of 164 patients (52 males) with primary hypothyroidism detected by a neonatal (TSH) screening program between 1997-2010. These patients were distributed as: athyreotic (Group B,n=48), ectopic (Group C,n=74) and eutopic (Group D,n=42). Also 8 patients with central hypothyroidism due to ßTSH defect (Group E) were included.
Results: Median age at diagnosis was significantly higher in Group A (90 days) and E (112 days) compared to Groups B,C and D (15, 15 and 17 days, respectively),$p< 0.0001$. Patients with CCH had freeT4 serum levels significantly higher median 0.68 ng/ml (range: 0.02-0.99) than patients with athyreosis median 0.15 ng/ml (range 0.03-0.51) and ßTSH defect median 0.1 ng/ml (range 0.06-0.28), $p< 0.001$, but not significantly different with ectopic or eutopic primary hypothyroidism median 0.6 ng/ml (range 0.03-1.5) and 0.74 ng/ml (range 0.03-1.66), p = NS).
Conclusions: Patients with CCH have a moderate impaired thyroid function as patients with ectopic or eutopic congenital primary hypothyroidism. Although the impact in neurocognitive development of this moderate thyroid dysfunction is still unknown, its presence in addition to the morbidities related to CMPHD raises a potential threat to postnatal central nervous system development and call for attention of this entity towards an earlier diagnosis.

P2-d1-1137 Thyroid 4

Comparison between liquid L-thyroxine (L-T4) solution and tablet in congenital hypothyroidism (CH)

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Background: Recently a liquid formulation of L-T4 has become available in Italy and this form is easier to administer to newborns than tablets.
Objective: We compared (case-control study):
- thyroid status during the first year of treatment
- psychomotor development (DQ) at 12 months of age
in 78 newborns with primary CH detected by neonatal screening using the two different L-T4 preparations (liquid and tablet form).
Population and/or methods: 78 pts were divided into two groups:
Group A: 39 pts who received liquid L-T4 solution in oral drops,
Group B: 39 pts who received L-T4 in tablet form.
TSH and fT4 were measured before therapy and after 7-10 days, 1-2 months, 3-5 months, 6-8 months and 9-12 months of treatment. L-T4 dose (mcg/kg/d) was also recorded at the same time points. DQ was assessed on the Griffiths mental development scales.
Results: The two groups did not differ regarding gestational age, birth weight, screening TSH, etiology and severity of CH, age at onset of therapy and median initial dose of L-T4. All pts achieved normalization of fT4 levels before 10 days of life, regardless of the kind of formulation (liquid L-T4 solution or tablet form) received. The study showed a normalization of TSH values after 7-10 days of therapy in 87% of pts treated with the liquid L-T4 solution and 82% of those who received the tablet form. Pts treated with the liquid L-T4 solution had significantly lower TSH values compared with those who received the L-T4 tablet form at 7-10 days ($p = 0.05$) and 6-8 months ($p = 0.043$) of treatment, despite a similar L-T4 dose; the value of fT4 was not different between the two groups during follow-up.
Mean DQ scores were within the average range in all pts.
Conclusion: These data confirmed the efficacy and safety of both formulations. The TSH inhibition trend when using liquid L-T4 may be linked to a higher absorption in comparison to the tablets. A tailoring of the L-T4 dose to the formulation and to the severity of CH is needed.

P2-d1-1138 Thyroid 4

Family satisfaction in an endocrine nurse specialist led congenital hypothyroid (CH) service

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Background: CH is usually managed by doctors, but nurses deliver this service in this centre. There is no published data on the quality of such a service.
Aim: To determine family satisfaction in a Congenital Hypothyroidism service (CH) delivered by endocrine nurse specialists.
Method: Families' perceptions of the quality of service provided in a nurse specialist led CH clinic were studied prospectively using a questionnaire given to 61 consecutive parents attending the clinic. The following questions were asked with regard to their experiences.
1. Were you provided with adequate information?
2. Were your concerns adequately addressed?
3. Were you able to ask questions that you wanted?
4. Did the nurse explain your child's condition adequately?
5. How satisfied were you with the education provided?
6. Can you contact your nurse when required?
7. How do you rate the communication regarding medication and test results?
8. How satisfied are you with your overall care?

Results:

Question	Responses (N)	Yes	No	Don't Know
Q1	61	53(87%)	6(10%)	2(3%)
Q2	61	52(85%)	6(10%)	3(5%)
Q3	61	60(98%)	1	
Q4	61	60(98%)	1	
Q5	58	Excellent-Good 50(82%)	Fair 7(11%)	Poor 1(1.6%)
Q6	54	Always 38(62%)	Sometimes 14(23%)	Never 2(3%)
Q7	60	Excellent-Good 52(85%)	Fair 6(10%)	Poor 3(5%)
Q8	59	Excellent-Good 57(93%)	Fair 2(3%)	

[Parent Responses to Questionnaires]

Conclusion: A nurse led Congenital Hypothyroid clinic delivers care that provides high satisfaction to parents.

P2-d1-1139 Thyroid 4

Pitfalls in the diagnosis of congenital hypothyroidism (CH)

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Background: In CH, thyroid imaging allows a precise characterization of etiology, which is an important factor in defining clinical management and long term outcome
Objective: To critically re-evaluate thyroid imaging in CH, especially to analyze thyroid US results, indications to scintigraphy in neonates and correlation between biochemical and instrumental data.
Methods: 115 babies from Emilia Romagna with raised capillary TSH (>10mU/L) on neonatal screening between Jan 2010 and Dec 2011 were recruited. They have made mandatory evaluation (complete history, physical examination,serum TSH, fT3,fT4) and thyroid US. In 23 babies 99mTc thyroid scan was performed. Exclusion criteria were preterm infants, malformed, babies with maternal thyroid disease or with a history of iodic excess.
Results: In 16 pts we found no correlation between the US and biochemical data. We performed scintigraphy that showed no radionuclide uptake in fossa. We re-evaluated carefully the US reports referred as hyperechoic tissue in thyroid fossa. Review showed definite features common to all the US images: - hyperechogenicity; -not globular aspect; -linear profiles of tissue (often triangular); -poor or excessive extension of tissue in fossa that makes impossible to use as distinguishing parameter the lateralization of large cervical vessels; -absence or inability to describe isthmus. In 1 of the these cases US report describes a tissue with isthmus, but scintigraphy did not showed either eutopic nor ectopic radionuclide uptake.
Conclusions: US is the best methodic in CH diagnosis but considerable experience is require to interpret US data. More sophisticated US machines improve the quality of information but require more knowledge, particularly if the tissue shows the characteristics mentioned above. The correlation with laboratory data is mandatory: if the US report and biochemical data are conflicting, the scintigraphy is the best methodic to define CH etiology.

P2-d1-1140 Thyroid 4

Fibroblast growth factor 21 (FGF21): a biomarker of mitochondrial diseases is increased in congenital hyperthyroidism and Hashimoto disease between endocrine diseases

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Background: Fibroblast growth factor 21 (FGF21) is a hormone that regulates glucose and lipid metabolism. Previous reports showed that serum FGF21 (sFGF21) levels were increased in patients with obesity and T2DM. No reports of sFGF21 level with endocrine diseases exist. Suomalainen, et al (2011) has reported that sFGF21 level was higher in mitochondrial diseases (MDs) than in non-mitochondrial muscular diseases, suggesting that serum FGF21 level is a new biomarker of MDs.
Objective and hypotheses: We confirmed whether
1) sFGF21 level has variability between endocrine diseases, and
2) sFGF21 level is higher in patients with MDs in the Japanese population.
Methods: We collected blood from patients with congenital hypothyroidism (n=45), growth hormone deficiency (n=25), Graves' disease (n=10), Hashimoto disease (n=5), precocious puberty (n=4), Hypochondroplasia (n=2), Turner syndrome(n=2), mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS, n=5), myopathy with A3243G mutation (n=8), carrier with A3243G mutation (n=4), Leigh encephalitis (n=2), Kearns-Sayre syndrome (n=1), carnitine transporter disorder (n=1), glycogen storage disease type III (n=1), Pompe disease (n=1), dermatomyositis (n=1). The control group was outpatients consulting for short stature but without abnormal findings (n=91). We used ELISA for sFGF21 level (BioVendor, Czech). Statistic analysis was performed with Man-Whitney test by Prism 5 (GraphPad, USA).
Results: sFGF21 levels were increased in congenital hypothyroidism, Hashimoto disease compared to the control. sFGF21 levels of MELAS, myopathy with A3243G, and carriew with A3243G had significantly difference compared to the control in the Japanese.
Conclusions: We showed that sFGF21 levels were increased in the Japanese patients with congenital hypothyroidims and Hashimoto disease between endocrine diseases, and as shown in previous reports, we could also see significant difference of sFGF21 in the Japanese MDs.

P2-d1-1141 Thyroid 4

Can an endocrine nurse specialist led service for congenital hypothyroidism (CH) deliver care in accordance with internationally accepted recommendations?

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Background: CH is usually managed by doctors, but nurses deliver this service in this centre after appropriate training. There is no published data on the adequacy of such a service.
Hypothesis: Specialist nurses can meet recommended care standards.
Method: All infants with CH at a single centre diagnosed between 2010 and 2012, managed in an endocrine nurse specialist led clinic after commencement of treatment by a doctor, were studied retrospectively. The timing and results of each patient's thyroid function tests was assessed to determine whether management was in accordance with published recommendations (Pediatrics 2006 Jun; 117(6):2290-303) which recommends that they be assessed
1) between 2-4 weeks after initiating treatment
2) every 1-2 months during the first 6 months of life
3) every 3-4 months between 6 months and 3 years
4) 4 weeks after changes in dose of levothyroxine
and that TSH level is < 5 mu/L by 2 weeks from start of therapy.
Reasons for failure to reach targets were determined.
Results: There were 49 infants (23 males) followed up for a mean (SD) of 10.2 months (±6.6) Forty three out of 44 patients (97%) met recommendation,
1. Twenty eight out of 30 patients less than 6 months of age (93%) met recommendation
2. Twenty one out of 23 patients aged 6 months-1 year (91%) and 100% of patients between 1 and 2 yrs of age met recommendation
3.Thirty seven out of 42 patients (88%) met recommendation
4. All the failures for recommendations1-4 were due to non-attendance. Ten out of 49 patients (20%) did not achieve target
5. All of them had initial treatment prescribed by a doctor and 5 were at < 15mg/kg/d of Levothyroxine which was beyond the control of the nurse.
Conclusion: A nurse led congenital hypothyroid service provides care in accordance with internationally recommended standards.

P2-d1-1142 Thyroid 4

Health-related quality of life in 10-year-old children with congenital hypothyroidism diagnosed by neonatal screening: the need for implementing patient reported outcomes in clinical practice

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Background: Much has been written about cognitive and motor development of children with congenital hypothyroidism (CH). However, less is known about the social and emotional consequences of growing up with CH.
Objective and hypotheses: To compare health-related quality of life (HRQoL) of 10-year-old children with CH with the general population.
Methods: A total of 82 children with CH and their parents completed several questionnaires addressing HRQoL. Children were classified as "severe" (n=41) or "moderate" (n=41) based on pre-treatment FT4 concentrations. Differences between children with CH and the general population were tested by analysis of covariance and one sample t-tests (mean scale scores HRQoL), chi-square tests and binomial tests (% at risk of impaired HRQoL).
Results: Children with CH reported lower mean HRQoL on motor, cognitive and social functioning, and on autonomy and positive emotions ($p < 0.0001$). Children with CH were also more often at risk for impaired HRQoL. No differences were found between the severity groups. Based on these finding we started the implementation of Patient Reported OutcomeS (PROS) using www.hetklikt.nu - an effective tool to monitor well-being over time, to detect problems at an early stage and to provide tailored interventions.
Conclusions: These results show that children with CH experience negative consequences in terms of HRQoL. Physicians should to be aware of these consequences and provide systematic attention and supportive care. The use of PROs in clinical practice can facilitate this.

P2-d1-1143 Thyroid 4

Allan-Herndon-Dudley syndrome caused by a novel *MCT8/SLC16A2* mutation in a Turkish family

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Background: The monocarboxylate transporter 8 (MCT8) was identified as a thyroid hormone transporter, and *MCT8/SLC16A2* mutations have been associated with Allan-Herndon-Dudley syndrome (AHDS), an X linked condition characterized by severe intellectual disability, global hypotonia, dysarthria, dyskinesias, and spastic paraplegia.
Objective: We report a 7.5-year-old intellectually disabled boy with a novel mutation in the *MCT8* gene associated with a characteristic neurodevelopmental phenotype with early childhood hypotonia. His laboratory evaluation disclosed elevated fT3 [6.29 pg/ml (normal range, 2.41-5.5)], low fT4 [(0.78 ng/dl (0.96-1.77)], and normal TSH [(4.42 μIU/ml (0.7-5.97)] levels. Serum

sex hormone-binding globulin (SHBG) levels were also increased [>180 nmol/L (13-71)].
Methods: Genomic DNA was prepared using a high-salt precipitation method from peripheral blood. Exons were amplified using exon specific primers tailed with M13 sequences to facilitate sequencing. Polymorphism studies of the alteration detected in exon 3 were carried out by sequencing normal control males and females. The 1000 genome and the Washington University NHLBI Exome Sequencing Project Exome Variant Server databases were used to see if the detected alteration was present.
Results: Sequencing analysis of the *MCT8/SLC16A2* gene identified a hemizygous G>A change at nucleotide 1201 (c.1201G>A) in exon 3, which results in a glycine being replaced by an arginine at amino acid 401 (p.G401R). This mutation was not observed in the SNP databases or in the controls indicating it is likely pathogenic and associated with the phenotype in the patient.
Conclusions: We identified a novel missense mutation in exon 3 of the *MCT8* gene in our AHDS patient, his mother and maternal grandmother. Analysis of the *MCT8* gene for mutations is suggested in intellectually disabled boys with increased free T3, low-normal to low free T4, and normal to elevated TSH levels and high serum SHBG levels.

P2-d1-1144 Thyroid 4

Interstitial deletion of the long arm of chromosome 2 in IgA deficiency and Graves disease

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Introduction: Interstitial deletions of the long arm of chromosome 2 are rare and characterized by multiple malformations, including craniofacial anomalies, epilepsy, developmental delay, and mental retardation, as well as growth retardation. There are no cases of interstitial deletion of 2q with autoimmune thyroid disease in the literature. Here we report on a patient with a 2q32.2-34 deletion, IgA deficiency and Graves' disease.
Case report: The patient is a male, term first child of healthy unrelated parents, being 32 years at delivery. There was no family history of malformations. He was delivered by Caesarean section at 38 weeks gestational age; birth weight 2,356g(-1.8SD), length 45.0cm(-1.9SD), head circumference 32.5cm(-0.5SD). He presented with muscular hypotonia, facial anomalies including high receding forehead, prominent beaked nose, divergent strabismus, bilateral ptosis, micrognathia. Sucking reflex was weak. A standard G-banded karyotype of peripheral lymphocytes showed an interstitial deletion of the long arm of chromosome 2; del(2)(q32.2q34). Global developmental retardation, epilepsy, dysphagia and eating disorder were apparent from early childhood. IgA deficiency was also detected within the first year of life. At the age of nine, he presented with severe watery diarrhea, fever and body weight loss. His height was 107cm(-4.2SD), and weight was 10.9kg. There was neither goiter nor exophthalmos. Blood tests showed hyperthyroidism (TSH < 0.01μIU/ml, FT3 16.27pg/ml, FT4 3.60ng/dl) and hypertonic dehydration. Antibodies, including TRAb, TSAb, TPO-Ab, were all positive. His maternal uncle had hyperthyroidism, but the details were unclear. Ultrasound scan showed approximately normal size of thyroid, indicating increased bloodstream. Treatment with methimazole improved diarrhea and thyroid function.
Conclusions: This is the first case report of interstitial deletion of the long arm of chromosome 2 with IgA deficiency and Graves' disease.

P2-d1-1145 Thyroid 4

Copy number determination of hypothyroidism genes by MLPA analysis in patients with hypothyroidism and thyroid hypoplasia

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Background: Genetic hypothyroidism presents a heterogeneous genetic inheritance: single allele mutation in genes with recessive pattern (pseudodominance), digenic inheritance and one phenotype/one mutation association were all observed, in particular in case of mild or complex phenotypes. Therefore it is necessary to screen multiple genes in order to identify the genetic defect and to help clinical management of these patients and families.
Objective and hypotheses:TSH receptor gene (TSHR) is the more frequent mutated gene in genetic hypothyroidism, so this represent the first target to be tested. If THSR gene sequence is normal, copy number determination of TSHR exons may be performed by MLPA analysis, together with other hypothyroidism genes. If hypothyroidism genes have normal dosage, their complete sequencing may be considerate.
Methods: From a large series of patients with hypothyroidism already screened for point mutation in TSHR gene by sequencing, we selected 22 patients with thyroid hypoplasia. 9 pts. presented congenital hypothyroidism and were positive at neonatal screening, 13 pts. were diagnosed as subclinical hypothyroidism (TSH>4.2 mU/liter) after neonatal period. To complete the search of causative mutations we performed copy number determination on genomic DNA from peripheral blood by MLPA analysis, with probes for TSHR gene and PAX8, TPO, FOXE1 and NKX2.1 genes.
Results: A deletion of TSHR gene exon 1 was identified in one allele in a patient, he was 6 yrs. old at first evaluation and presented TSH level up to normal range in more than two tests.
Conclusions: Our results confirmed the primary role of TSHR gene mutations in hypothyroidism and the necessity of copy number determination of hypothyroidism genes in diagnostic steps. We intend to extend the MLPA analysis in all the patients with suspected genetic hypothyroidism, and to proceed with PAX8 gene sequencing in negative cases to improve the mutation detection of this heterogeneous disease.

P2-d1-1146 Thyroid 4

A novel NKX2.1 mutation in a family with congenital hypothyroidism (CH)

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Background: Mutations in the NKX2.1 gene have been reported in numerous patients with brain-thyroid-lung syndrome.
Methods: We present the case of a 30- year- old mother and her 6-year-old son with congenital hypothyroidism both diagnosed by neonatal screening. The mother developed mild chorea at the age of 7 months and acute respiratory failure during an H1N1 virus infection two years ago. Her boy presented soon after his birth acute respiratory distress and demonstrated very early severe choreoathetosis and mental retardation.
Results: The NKX2-1 gene was sequenced and the novel monoallelic mutation c.1597_insG was identified in the affected mother and son. The functional effect of this novel mutation was characterized in silico by using the PIC (protein interactions calculator), a server which categorizes various protein interactions. The structural analysis of the wild type open and closed conformations of NKX2.1 was compared alone and in the presence of c.1597_insG and demonstrated that it causes structural conformational changes that lead to the destabilization of the functional properties of the protein. In conclusion, we describe a novel NKX2.1 mutation which produces variable phenotypes in the affected members of the same family.
Conclusions: Our preliminary results suggest that with the comparison of existing neighboring mutations a better understanding of the functional role of distinct NKX2.1 components could be delineated. Additional studies are required to clarify the complexities of genotype/phenotype correlations of the identified c.1597_insG in the NKX2-1 deficiency syndrome.

P2-d2-1147 Thyroid 5

Prevalence of renal and cardiac abnormalities in children with congenital hypothyroidism

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Background: Congenital hypothyroidism is the most common congenital endocrine disorder. Common transcription factors seem to be involved in the development of thyroid, kidney and heart.
Objective: We investigated the prevelance of congenital heart disorders, renal and urinary system abnormalities in children with congenital hypothyroidism.
Patients and methods: Eighty nine patients (43 girls) with congenital hypothyroidim were involved in this study. Thyroid function tests, thyroid ultrasounds were performed in all patients. Echocardiography and urinary system ultrasounds were performed in 80 and 53 patients.
Results: At diagnosis mean age was 0,33±0,56 years, mean TSH level was 51,9 ± 41,3mIU/ml. Thyroid agenesis, hypoplasia and ectopic thyroid were diagnosed in 5,6%(n=5) , 3,3%(n=3), and 4,5% (n=4) of the patients respectively. There was no patient with central hypothyroidism. Congenital heart disorders were determined in 7,5% (n=6) of the patients. One secundum type atrial septal defect, 1 ventricular septal defect and aort stenosis, 2 patent ductus arteriosis, 1 aort insufficiency, and 1 Fallot tetralogy were diagnosed. Only in the patient with aort insufficiency thyroid was ectopic. Urinary system abnormalities were determined in 11,3%(n=6) of the patients. One left renal agenesis, 1 bilateral pelvi caliceal dilatation, 1 double collecting system, 1 renal paranchymal cyst, and 2 nephrolithiasis were diagnosed. Only in the patient with double collecting system thyroid was hypoplastic. None of the patients with urinary system abnormality had cardiac disorder.
Conclusion: This study showed that the frequencies of congenital heart disorders and urinary system abnormalities are increased in the patients with congenital hypothyroidism compared to normal population. Future studies with higher numbers of patients with congenital hypothyroidism will show whether routine investigation of cardiac and urinary system abnormalities is mandatory in these patients.

P2-d2-1148 Thyroid 5

Three cases of congenital central hypothyroidism in two families with TSH and prolactin deficiency caused by *IGSF1* mutation

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Introduction: Congenital central hypothyroidism (CCH), characterized by insufficient TSH secretion resulting in low levels of thyroid hormones, are rare disorders. Despite the severity of hormonal dysfunction, congenital disorders of the hypothalamo-hypophyseal system are seldom diagnosed in early infancy. Recently, Yu et al. reported a new responsible gene, *IGSF1*, which causes X-linked CCH. We report three male pediatric patients in two families having congenital hypothyroidism with TSH and PRL deficiency, detected by FT4 and TSH newborn screening.
Case 1: A boy was born at week 38 of gestation and weighted 3.17kg. Thyroid screening results at 5 days of age revealed TSH 5.6 mU/l, FT4 0.07 ng/dl. Epiphysis of the distal femur was not detected. No other symptoms were observed. L-T4 treatment was started at the age of 22 days followed by a TRH loading test. Retesting was performed at 6 years after discontinuation of L-T4. Serum TSH 4.6mU/l, PRL 1.0 ng/ml, FT4 0.13 ng/dl at baseline and a low delayed response of TSH were observed after TRH loading. Moreover one of maternal cousin was diagnosed as CCH, however; his thyroid function is milder.
Case 2: A boy was born at week 38 of gestations and weighted 3.37kg. Thyroid screening at 5 days of age revealed TSH 5.9mU/l, FT4 0.14 ng/dl. Epiphysis of the distal femur was 1 x 3 mm. L-T4 treatment was performed at 5 years after discontinuation. Serum TSH 2.8mU/l, PRL 1.1ng/ml, FT4 0.1ng/dl at baseline and a low delayed response of TSH were observed after TRH loading. Their growth and development were normal. MRI of the pituitary region was also normal. PCR-based direct sequencing of all coding exons of *IGSF1* revealed a novel mutation affecting the essential splice site (c.2014+1G>A) in case 1. As for Patient 2, we could not amplify exons 14 to 19 by PCR, which suggested exon-level deletion involving *IGSF1*. Clinicians should consider *IGSF1* mutations when a boy presented CCH accompanied by PRL deficiency.

P2-d2-1149 Thyroid 5

Longitudinal study on thyroid function in patients with thalassemia major: high incidence of central hypothyroidism by 18 years

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Background: Hypothyroidism is one of the most frequent complications observed in patients suffering from thalassemia.
Objective: We investigated and reviewed the thyroid function in all thalassemic patients attending the Pediatric Endocrine Clinic of HMC, Doha, Qatar during the last 12 years of follow up.
Methods: 48 patients with ß-thalassemia major between 5 and 18 years of age. Thyroid dysfunction was defined as follows: overt hypothyroidism (low FT4 and increased TSH levels >5 µIU/ml); subclinical hypothyroidism (normal FT4, TSH between 5-10 µIU/ml) and central (secondary) hypothyroidism (low FT4 and normal or decreased TSH)
Results: During this period hypothyroidism (HT) was diagnosed in 17/48 (35%) of patients. There was no significant difference in prevalence in males 7/22 (32%) versus females 10/26 (38%). 16 /48 had hypothyroidism after the age of 10 years. The prevalence of overt HT had risen from 0 % at the age of 7 years to 35% at the age of 18 years. None of the patients had high anti-thyroperoxidase (TPO) antibody titers. Thirteen out of the 17 patients with HT, had normal or low TSH level (not appropriately elevated) indicative of defective hypothalamic pituitary response to low FT4 (central HT). Three patients (6.3%) had subclinical hypothyroidism (TSH between 5 and 10 uIU/ml and normal FT4). The general trend of free thyroxine level showed progressive decrease over the 12 years, whereas TSH levels did not show a corresponding increase. These data suggested defective hypothalamic pituitary thyroid axis involving both TSH and FT4 secretion in patients with TM over time. There was a significant negative correlation between serum ferritin and FT4 ($r = -0.39$, $p = 0.007$) but no correlation was found between ferritin and TSH.
Conclusions: Worsening of thyroid function was observed in 35 % of the studied thalassemic patients by the age of 18 years. Results indicated high incidence of defective pituitary thyrotrophic function.

P2-d2-1150 Thyroid 5

Glutathione peroxidase and selenoprotein P levels in children and adolescents with Hashimoto thyroiditis and subclinical hypothyroidism

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Background: Selenoproteins contain selenocysteine and are responsible for biological functions of selenium. Several selenoproteins are expressed in the thyroid. Thyroid hormones regulate selenoprotein expression. Glutathione peroxidase (GPx) is one of the major selenoproteins which takes advantage of the chemical properties of selenium to catalyze removal of hydroperoxides by glutathione. GPx is important in preventing the thyroid cells from oxidative damage. Selenoprotein P (SeP) is considered as the plasma selenium transporter to tissues.
Objective and hypotheses: The aim of this study was to evaluate GPx and SeP levels and their correlation with thyroid hormones, TSH, anti-thyroperoxidase (TPO-Ab) and anti-thyroglobulin (Tg-Ab) antibodies in children and adolescents with Hashimoto's thyroiditis (HT) and subclinical hypothyroidism (SH) and their comparison with normal subjects.
Methods: Blood samples were collected from 32 HT, 20 SH, and 25 matched normal subjects. Thyroid hormone levels were normal in all subjects. GPx enzyme activity was measured by spectrophotometry at 340 nm. SeP, TPO-Ab, and Tg-Ab were determined by ELISA kits. T_4, T_3, T_3 uptake and TSH were also measured. Analysis of variance (ANOVA) and student t-test were used to compare means in different groups.
Results: GPx activity was not significantly different in HT and SH patients compared to normal subjects (54.64±14.5, 47.6±7.03, and 54.58±13.8 U/g Hb, respectively). SeP did not differ significantly in HT, SH and normal subjects (23.37±10.6, 19.33±8.3, and 20.61±12.0 ng/ml, respectively). GPx and SeP were both lower in SH subjects compared to HT and normal subjects but the difference was not significant. We did not find any correlation between GPx or SeP with TPO-Ab or Tg-Ab. SeP in female subjects was significantly lower than that in male subjects.
Conclusions: Results show that GPx and SeP levels are not different in HT and SH compared to normal subjects.

P2-d2-1151 Thyroid 5

Follow-up study of thyroid function after oncologic treatment in children

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Background: The length of patient survival after cancer treatment is increasing and, in some cases, does not differ from the average life span in healthy individuals. Thyroid disorders are usually diagnosed during the cancer disease, when the thyroid gland is being destroyed by the tumor or surgical treatment. The effects of radio- and chemotherapy appear and progress at a slow rate within the next few years.
Objective and hypotheses: The aim of the study is evaluation of thyroid function in long-term follow-up after oncologic treatment.
Methods: We were investigated 157 patients ages 16-25 years. Patients were observed 4-19 years after the end of oncologic treatment (median: 10 years). 66 children and young adults within the same age group were examined as the control group in this study.
TSH, fT4, fT3 levels, TPO Ab and TG Ab, TSI Ab and the ultrasonography of the thyroid gland were investigated in all children.
Results: The percentage of thyroid diseases in patients after oncologic treatment.

	Number of patients	AITD	Graves' disease	Hashimoto's thyroiditis	Nodules of the thyroid with diameter >5mm
All patients	157	7,0	1,3	5,7	12,7
Control Group	66	7,6	1,5	6,1	0

[The percentage of thyroid diseases]

AITD were observed more often in the control group than in children after oncologic treatment. The levels of antithyroid antibodies did not correlate with doses of antracycline, X-rays or BMT.
Statistically significant more often thyroid nodules were observed in patients after oncologic treatment. The nodules directly correlated with X-ray doses. Additionally 2 patients were diagnosed with thyroid papillary cancer.
Conclusions: Oncologic treatment is not involved in AITD development, but in 10 years that followed, increased risk of thyroid nodules and thyroid cancer development were observed.

P2-d2-1152 Thyroid 5

Vitamin D deficiency in autoimmune thyroiditis

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Background: In addition to calcium homeostasis vitamin D also plays an important role in supressing autoimmune diseases. In this study vitamin D status in the patients with autoimmune thyroiditis were evaluated.
Patients and methods: One hundred patients(72 female, 49 pubertal) with chronic autoimmune thyroiditis(CAT) were involved.
Increased serum anti-thyroid peroxidase and/or anti-thyroglobulin levels with heterogenous thyroid gland image in ultrasonography and high serum thyroid receptor stimulating antibodies indicated the diagnosis of CAT and Graves disease respectively. Vitamin D levels < 30 ug/L was defined as insufficiency and < 20 ug/L as deficiency. Serum vitamin D levels of patients were compared with age matched healthy control group.
Results: CAT and Graves disease were diagnosed in 87 and 13 patients. Mean age at the time of diagnosis was 12,36 ±3,22years. Hypothyroidism was found in 18 patients (all CAT) and 8 patients had hyperthyroidism (all Graves disease).In all of the patients mean 25-OH vitamin D level was 18,08 ± 13,71 ug/L. Mean vitamin D values were 16,09±9,73ug/L and 19,14±11,77 ug /L for CAT and Graves disease. Mean Vitamin D level for the healthy control group was 21,32 ± 9,49 ug /L. Compared to controls patients with autoimmune thyroiditis had significantly low serum D levels ($p< 0,01$).Vitamin D deficiency and insufficiency were identified in 70%, and 86 % of the patients. Vitamin D levels were < 10 ug/L in 29, between 10-20 ug/L in 43 , and between 20-30 ug/L 16 patients. Only 12 patients had vitamin D levels >30 ug/L.
Conclusion: Vitamin D deficiency and insufficiency were determined in the majority of the patients with autoimmune thyroidits. Since how and how much does vitamine D act on autoimmune diseases is unknown, it's clear that new studies on this topic are essential.

P2-d2-1153 Thyroid 5

Resistance to thyroid hormone in two generations with de-novo mutation traced to a mutation in ancestral germline - report of the first Croatian family

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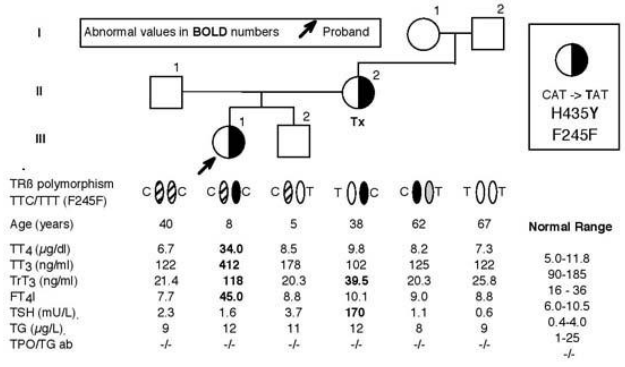
Introduction: Resistance to thyroid hormone (RTH) is primarily dominantly inherited and characterized by reduced organ responsiveness to thyroid hormone with elevated serum iodothyronines and unsuppressed TSH levels. It is most frequently caused by thyroid hormone receptor beta (*THRB*) gene mutations.
We report a child and her mother with de-novo missense mutation in the *THRB* gene (H435Y) traced to a mutation in ancestral germline.
Case study: A 7.5-yr-old girl presented with goiter. Parents report nervousness poor weight gain despite good appetite and occasional palpitations. Her weight was 24.9 kg (50 c.), height 138.3 cm (>95 c), heart rate 81/min, palpable goiter and warm and wet skin. Serum iodothyronines were elevated with a normal TSH suggesting RTH (Figure 1). There was perceptive hearing loss at 30dB.
Her mother presented at age 12 years with symptoms of hyperthyroidism; paroxysmal supraventricular tachycardia and goiter. Diagnosis of Graves' disease, despite unsuppressed TSH suggesting RTH, led to antithyroid drug treatment, followed by thyroidectomy at the age of 14 years and subsequently levothyroxine therapy.
Sequencing of the *THRB* gene revealed a single nucleotide substitution producing the missense mutation H435Y in both proband and her mother. Genotyping of the maternal grand parents revealed that the mutation in the mother originated de-novo in the *THRB* allele inherited from the maternal grand mother (Figure 1).



[Figure 1. Pedigree of the family]

Conclusion: We present the occurrence of RTH in two generations caused by *THRB* H435Y traced to a de-novo mutation in an ancestral allele. To our knowledge this is the first report of a *THRB* gene mutation in Croatia.

P2-d2-1154 Thyroid 5

Effects of two years L-thyroxine therapy on bone status in children with idiopathic subclinical hypothyroidism

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Background: Subclinical hypothyroidism (SH) is defined by serum TSH concentration above the upper limit of the reference range and serum free T4 (FT4) level within normal range. The management of SH still represents a clinical dilemma. Despite thyroid hormones and TSH play an important role in skeletal growth and bone homeostasis, data on bone status in SH are contrasting. In children SH does not impair bone health, however the effects of L-Thyroxine (L-T4) replacement therapy have never been evaluated.
Objective and hypotheses: To evaluate the effects of L-T4 therapy on bone health in children with SH.
Methods: Fifteen children (7 M) aged 10,6±4,3 years with idiopathic SH were studied before and after two years of L-T4 therapy (mean dose 1,5±0,9 µg/kg/die). Serum TSH and FT4 were evaluated at entry and every 4-6 months. Dual-energy X-ray densitometry (DXA) to evaluate lumbar spine bone mineral density (BMD) and quantitative ultrasound (QUS) at proximal phalanges of non-dominant hand to assess bone quality, measured as amplitude-dependent speed of sound (Ad-SoS) and bone transmission time (BTT), were performed at entry and after 2 years of L-T4 therapy. Fifteen healthy children, sex- and age-matched, were enrolled as controls.
Results: No differences in bone parameters were observed between SH patients and controls at study entry and between SH patients before and after L-T4 therapy (Table).

	Controls	SH at entry	SH after L-T4	p[a]	p[b]
TSH (mU/l)	2,8±0,7	6,7±1,7	3,1±1,5	< 0,0001	< 0,0001
FT4 (ng/dl)	1,3±0,1	1,2±0,3	1,3±0,2	Ns	Ns
BMD Z-score	-0,02±0,9	-0,05±1,3	0,4±1,2	Ns	Ns
Ad-SoS Z-score	0,2±1,3	0,3±1,3	0,1±1,2	Ns	Ns
BTT Z-score	-0,8±2,0	0,2±1,0	0,5±0,9	Ns	Ns

[a SH entry vs Controls; b SH entry vs after L-T4]

Conclusions: Untreated SH in children does not impair bone health and TSH normalization, after 2 years of L-T4 therapy, does not improve bone status.

P2-d2-1155 Thyroid 5

The occurrence of Evans syndrome during remission of Graves disease

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Introduction: The association between Graves' disease and Evans syndrome has been reported by a number of authors. In most cases, Evans syndrome coincided with Graves' disease or occurred during the treatment with an antithyroid drug. However, there are few cases of autoimmune hemolytic anemia and thrombocytopenia occurred without thyrotoxicosis in Graves' disease. We report the case of occurrence of Evans syndrome during remission of Graves' disease.
Case study: A 11-year-old girl who had been diagnosed as Graves' disease was admitted with severe hemolytic anemia and mild thrombocytopenia. She had been treated with methimazole for Graves' disease for 2 years and 6 months before admission, she discontinued taking medication because of remission. Laboratory findings showed hemoglobin of 4.5 g/dL, hematocrit of 13.6%, reticulocytes of 22.2%, platelet count of $105\times10^3/\mu L$, total bilirubin of 6.60 mg/dL and strong positive for direct and indirect Coombs' tests, respectively. Peripheral blood smear revealed spherocytosis, reticulocytosis and thrombocytopenia. Thyroid function tests indicated a euthyroid state, as both free T4 and TSH were normal. Anti-thyroglobulin antibody and peroxidase antibody were elevated but TSH receptor antibody was 10.7% (normal range; < 15%). Antinuclear antibody was positive (1:160, homogeneous pattern). The patient was started on prednisolone 1 mg/kg/day and gradually tapered off. 7 days after admission hemoglobin has improved to 6.0 g/dL and platelet had decreased to $86\times10^3/\mu L$. 26 days after admission, hemoglobin was 11.3 g/dL and platelet was $165\times10^3/\mu L$.
Conclusion: Although the mechanism underlying Evans syndrome associated with Graves' disease remain uncertain, the present case suggests that both conditions may have a common autoimmune mechanism, not just association with thyrotoxicosis.

P2-d2-1156 Thyroid 5

Diagnostic and predictive value of ultrasound and isotope thyroid scanning, alone and in combination, in infants referred with thyroid stimulating hormone elevation on newborn screening

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Background: Accurate, early diagnosis of infants referred with TSH elevation on newborn screening is required for appropriate counselling, selection of patients requiring molecular genetic study, and deciding on medium/long term management.
Aim: To determine the predictive value of thyroid ultrasound and radioisotope scanning (USS & RIS), alone and in combination, in the initial diagnosis of newborn infants with TSH elevation.
Design: Retrospective blind review of USS and RIS images followed by consensus final diagnosis based on clinical features, biochemistry, imaging and mutation analysis.
Results: Between 2004 and 2011 inclusive 97 infants (64F:35M) with capillary TSH elevation BW 3.38(2.04-4.86)kg & gestation 40(33-42)weeks, underwent successful thyroid USS and RIS (99mTc) in a single centre. Final diagnostic breakdown was thyroid dysgenesis due to ectopia (38), athyreosis (19) and hypoplasia in situ (4); thyroid dyshormonogenesis (20); transient TSH elevation (12) and status still uncertain (4).Combined scanning at the initial visit resulted in a correct final diagnosis in 77/97 (79%) cases. RIS was 100% specific and sensitive for ectopia and 100% sensitive for athyreosis but showed absent uptake in 6 infants with an in situ gland (81% specificity). USS showed ectopia in 21/39 patients (55% sensitivity and 100% specificity), with only 54% specificity for athyreosis. For thyroid dyshormonogenesis RIS and USS were 89% and 90% specific and 80% and 95% sensitive but 100% sensitive if combined. By contrast neither modality, alone or in combination, could predict final diagnosis in 12 infants with non-enlarged eutopic glands.
Conclusion: Dual thyroid scanning is highly effective in making a definitive diagnosis in newly referred infants with TSH elevation. USS cannot reliably detect thyroid ectopia while RIS may be misleading in showing no uptake despite the presence of a gland in situ. RIS and USS are complementary in the assessment of eutopic glands.

P2-d2-1157 Thyroid 5

Personalised replacement therapy (RT) with L-thyroxine (T4) + L-triiodothyronine (T3) in congenital hypothyroidism (CH)

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Background: T4 monotherapy is traditionally the treatment of choice for hypothyroidism. Recently it was proposed T4 + T3 RT in T4 treated adults with hypothyroidism observing the lack of well-being despite normal range TSH levels.
Objective and hypotheses: Among > 400 patients with CH diagnosed by TSH screening of 1,369.503 newborns since 1982 increases the number of children with hypothalamo-pituitary resistance to thyroid hormones (high TSH values despite progressively increasing T4 intake and free T4 levels), who had earlier normal thyroid parameters for years and years. The aim of this study was to analyze the effect of T4 + T3 combination on their thyroid parameters.
Patients: 8 girls + 8 boys (age: 11,9 +/- 6,3 yrs) were included with increased, insuppressible TSH values (15,7 +/- 5,7 mIU/L) despite their high free T4 (FT4) level (21,16 +/- 2,5 pmol/L, and normal free T3 (FT3) values (5,7 +/- 0,84 pmol/L) at the last three visits before introduction of T3 administration.
Results: 0,18 +/- 0,09 mcg/kg/day T3 was given once a day without adverse events. The short period results (TSH: 4,2 +/- 3,15 mIU/L; FT4: 16,85 +/- 3,1 pmol/L, and a moderate increase of FT3: 7,4 +/- 1,8 pmol/L) were confirmed after longer period (2,9 +/- 2,0 yrs) with further improvement of the parameters. The T4 dose decreased during the combined RT significantly (from 2,6 +/- 0,9 to 2,18 +/- 0,6 mcg/kg/day); the T4:T3 ratio proved to be between 5:1 and 19:1; the FT4/FT3 quotient normalized (from 3,8 +/-0,4 to 2,6 +/- 0,3).
Conclusions: There are children and adolescents with CH, who need T3 administration due to the development of reversible hypothalamo-pituitary resistance to T4 during their permanet RT. The small dose of T3 was able to normalize the TSH and T4 level with a moderate elevation of FT3 values. The pathomechanism of this reversible resistance and the efficacy of T3 administration need further studies especially in relation to the possible disturbance of deiodination.

P2-d2-1158 Thyroid 5

Neurodevelopmental outcomes in children with congenital hypothyroidism treated with high-dose initial replacement and close monitoring

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Background: Despite newborn screening and early levothyroxine (LT4) replacement there are continued reports of mild neurocognitive impairment in children with congenital hypothyroidism (CHT) identified by neonatal screening programs. In Auckland, New Zealand, cases are identified by a neonatal screening program with rapid institution of high initial dose LT4 replacement (10-15mcg/kg/day). This produces rapid normalisation of thyroid function.
Objective and hypotheses: Rapid identification and high initial dose replacement can prevent even subtle impairment of intellectual and motor development.
Methods: CHT cases and their sibling controls were enrolled and underwent assessment of IQ using the WPPSI IV or the WISC IV depending on age and motor development and visuomotor integration using the Movement Assessment Battery for Children and Beery Visuomotor index respectively. The effect of severity was assessed by comparing CHT patients based on aetiology and initial TSH concentration. Groups were compared using linear mixed models, controlling for age, sex, parental intelligence (measured at the same time as their children) and socioeconomic status..
Results: 44 CHT cases and 53 sibling controls were enrolled and underwent all assessments. There was no difference in overall IQ between CHT cases and controls (95.2 vs 98,6; p=0.20). Similarly no tests of motor function were worse in the CHT group. There was an association between longer time to normalise T4 and worse balance. Severity of CHT based on either initial TSH or aetiology did not influence outcome.
Conclusions: If infants with CHT are rapidly identified and treated with high dose LT4 replacement, intellectual and motor impairment can be prevented. Treated this way, severity does not affect outcome, however time taken to normalise T4 has a subtle negative impact on motor function, underlining the importance of high initial starting dose.

P2-d3-1159 Thyroid 6

The main features of thyrotoxicosis in prepubertal children

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Background: Graves' disease (GD) is the most frequent cause of thyrotoxicosis in children. Pathology manifestation usually occurs in adolescence.
Objective and hypotheses: To determine the clinical and laboratory features of thyrotoxycosis progression and treatment in prepubescence compared with pubertal and postpubertal children.
Method: 35 children with GD in the endocrinological department of University hospital (n of prepubescence (the 1st group): puberty (2nd): postpu-

bertal phase (3rd)=5:20:10) were retrospectively analyzed over the 2005-2012 years.
Results: Irritability was the main complaint in prepubertal patients (60%) related to pubertal and postpubertal children (5 and 20% respectively,p< 0.005). Thyroid volume was more increased above the age norms in prepubertal patients (212.6±151.8%) than in postpubertal (106.2±208.8%) and pubertal (142.1±103.9%,p< 0.05). Thyrotoxycosis tended to severe onset in prepubertal children regard to pubertal and postpubertal: FT_4 and TSH were 94.9±38.6pmol/L and 0.08±0,067µIU/l in the 1st group (51.9±20.2 and 0.1±0.2 in the 2nd; 51.6±29.9 and 0.04±0.06 in the 3rd one, respectively p>0.05). AtTPO were increased regardless of the stage of puberty (1st-580.25±425.87IU/ml, 2nd-430.4±497.87, 3rd-511.08±376.79,p>0.05). TSH receptor antibodies were elevated from the 1st to the 3rd groups properly (14.8±9.4IU/ml, 18.6±10.9 and 12.7±18.4,p>0.05).
All patients were administered antithyroid drug monotherapy in the initial stage of treatment. Medicine dosage was higher in the 1st group-0.8±0.2 mg/kg/day (0.5±0.54 and 0.4±0.09 in the 2nd and 3rd respectively,p< 0.01).
Conclusions: Irritability was the main complaint in prepubertal patients. Thyrotoxicosis in prepubertal period was characterized by greater goiter (p< 0.05), the highest levels of FT_4 and TSH suppression (p>0.05) tendency; higher doses anthithyroids (p< 0.01) were used in therapy.

P2-d3-1160 Thyroid 6

Twins with hypothyroidism and Papillon-Lefevre syndrome

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Background: Papillon-Lefevre syndrome (PLS), first described in 1924, is a very rare syndrome characterized by palmoplanter hyperkeratosis and precocious, rapidly progressive exfoliation of primary and permanent dentition. Hypothyroidism has not been previously reported as a feature of PLS. We report twins with PLS and hypothyroidism suggesting genetic and/or immunological relationship.
Case report: The twin sisters are 8 years old. Both initially presented with erythaematous palmoplanter rash which later changed into hyperkeratosis. Twin 1 was incidentally diagnosed with hypothyroidism at the age of 6 months when investigated for a small stature while twin 2 was eventually diagnosed with hypothyroidism on further screening. By 5 years of age, both of the twins only had 2 premolar teeth left. They required full dentures because they lost all of their teeth by the age of 8 years. They are on thyroxin treatment and fortunately both are developmentally normal.
Discussion: The cause of PLS is not fully understood. Genetic, immunologic and microbiologic causes have been proposed. Loss of function mutations in the Cathepsin-C gene located in chromosome 11q14.1-q14.3 has been described. Autoimmune hypothyroidism was reported in an adult with palmoplanter keratoderma and the skin manifestations have improved with thyroxin treatment. However, hypothyroidism is not a known association with or previously reported as a feature of PLS. These twins have both of the conditions. Dyshormonogenesis is the likely cause of hypothyroidism in the twins because the thyroid glands were detected in the normal place in both by USS and tests for anti thyroid antibodies were negative. We postulate a genetic relationship, though we could not confidently rule out immunological triggers, between PLS and hypothyroidism.
Conclusion: Further genetic studies of the cause of hypothyroidism in these children are arranged and it may unveil a hidden relationship between PLS and hypothyroidism.

P2-d3-1161 Thyroid 6

The incidence and characteristics of thyroid nodules in congenital hypothyroidism in infants

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Background: Thyroid nodules are extremely rare in children before puberty (1.5% or less) and are usually incidentally detected mass. Some reports revealed that risk of thyroid nodules is increased in children with congenital hypothyroidism due to dyshormonogenesis or an iodine transformation defect. But there have been few comprehensive studies detailing characteristics of thyroid nodules in infant with congenital hypothyroidism.
Objective and hypotheses: To estimate the incidence and characteristic of the thyroid nodules with congenital hypothyroidism in infant.
Methods: We retrospectively reviewed the medical records of congenital hypothyroidism patients in our center from January 2003 to December 2012. Data of 662 pediatric patients (mean age, 6.4 weeks, 1-48 weeks; male to female ratio, 1:1.31) who underwent ultrasonography (US) were reviewed.
Results: Thyroid nodules were presented in 4.0% (twenty-seven of 662) of cases. US showed colloid cystic nodules in 17 patients, solid nodules in 10 patients. The mean diameters of solid nodules were 3.8±1.4 (range: 2.0-7.0 mm), cystic nodules were 2.8±1.1 (range: 2.0-5.0 mm). The final subtypes of congenital hypothyroidism were hypoplasia (n=20), dyshormonogenesis (n=2), transient elevated TSH level (n=4), maternal antibody-induced congential hypothyroidism (n=1). All patients were treated with levothyroxine adjustment. Follow-up US was performed in 18/27 patients. At follow-up, 11 nodules (61.1%) were completely disappeared and 2 nodules decreased in size.
Conclusions: Thyroid nodules and cystic lesions with congenital hypothyroidism in infant are often thought to represent benign condition. Our study, which is the first study in the literature to specifically thyroid nodules in infant, shows that US is useful in evaluating thyroid nodules in single center.

P2-d3-1162 Thyroid 6

Long-term outcomes of paediatric Graves disease

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Background: Long term remission rates in pediatric Graves' disease are lower in children compared to adults. Remission is achieved in less than 30% cases after initial course of antithyroid drugs (ATDs). There are no uniform recommendations for indications and choice of definitive treatments like radio-iodine ablation (RAI) or surgery. RAI is being increasingly used and has been shown to be safe.
Objective: We studied long term outcomes of pediatric onset Graves' disease seen at our center and factors associated with need for definitive therapy.
Methods: Sixty six patients (58 females, 8 males) with Graves' disease diagnosed < 18 years of age and with duration of ≥2 years since diagnosis were included. Medical records were reviewed for clinical details at onset, investigations and treatment received. Current symptoms, investigations and treatment details were recorded by telephonic interview of patients. Outcomes of initial course of ATDs, factors associated with need for permanent therapy, persistent goiter, persistent opthalmopathy and need for permanent thyroxine replacement were studied.
Results: Median age at diagnosis was 13 years (range 3.5-17 years) and duration since diagnosis was 7 years (range 2-30 years). Outcomes of initial course of ATDs included long term remission (> 2 yr), failure of remission and relapse after initial remission in 12.3%, 21.5% and 66.5% respectively. Forty four patients (67.7%) were managed with definitive therapy. Initial free T4 and thyrotropin receptor antibody (TRAB) levels were significantly higher in those who required definitive therapy. Long term sequelae included need for thyroxine replacement (64.6%), persistent goiter (18.5%) and persistent opthalmopathy (29.7%).
Conclusions: Long term remission rates with initial ATDs are very low especially with longer follow up and majority of the patients relapse. Higher free T4 and high titer of TRAB predict the need for definitive therapy.

P2-d3-1163 Thyroid 6

Establishment of reference ranges for thyrotropin, thyroxine, free thyroxine, triiodothyronine and T-uptake in neonates and infants

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Background: Pediatric healthcare is critically dependent on the availability of accurate and precise reference intervals to allow appropriate clinical interpretation.
Objective and hypotheses: To obtain reference intervals for TSH, T4, fT4, T3 and T-Uptake in a pediatric population from Córdoba, Argentina.
Methods: Serum samples of 807 healthy neonates and infants (age range 2 to 365 days) were analyzed using electrochemiluminescent immunoassay (cobas e 601).
Results: No significant differences were observed between the sexes. The percentile 2.5th, 50th and 97.5th were calculated for all reference groups. The TSH, T4, fT4, T3 and T-Uptake levels are shown in table 1.

		TSH (uIU/mL)	T4 (ug/dL)	fT4 (ng/dL)	T3 (ng/dL)	T-Uptake
Days	n	2.5th - 97.5th	2.5th - 97.5th	2.5th - 97.5th	2.5th - 97.5th	2.5th - 97.5th
2-14	77	0.80 - 8.29	7.4 - 19.1	1.3 - 2.9	137.5 - 321.1	0.8 - 1.1
15-29	98	1.15 - 7.61	7.3 - 16.4	1.1 - 2.0	124.4 - 314.6	0.7 - 1.2
30-89	419	0.85 - 7.79	7.3 - 17.7	1.0 - 2.1	141.9 - 365.6	0.9 - 1.3
90-365	213	0.80 - 7.17	7.1 - 17.0	0.9 - 2.1	142.1 - 370.6	0.8 - 1.3

[Table 1: TSH, T4, fT4, T3 and T-Uptake percentiles]

Conclusions: We report pediatric reference intervals for TSH, T4, fT4, T3 and T-Uptake. It should assist pediatricians in interpreting these hormonal results more accurately and thereby lead to improve diagnosis of childhood thyroid diseases. Our results reveal that physiological behavior of TSH, T4 and fT4 levels is similar in the four age groups, showing a tendency to decrease at one year of life, whereas T3 values are slightly higher than in the neonatal period and remain high. This behavior can be the result of different mechanisms, including an increased tissue activity of type I deiodinase and the "reset" of the hypothalamic hypophyseal "set point" for the control of TSH.

P2-d3-1164 Thyroid 6

Clinical utility of thyroid scans in mild neonatal hyperthyrotropinaemia

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Background: Mild neonatal hyperthyrotropinemia (MNH) is characterized by an abnormal newborn screen (NBS), followed by mildly elevated TSH and normal FT4 on confirmatory tests. The literature on MNH is sparse, and no studies have assessed the prognostic value of thyroid scintigraphy in infants with MNH.
Objective and hypotheses: Examine the utility of information provided by thyroid scintigraphy for management of infants with MNH.
Methods: Retrospective study of infants with MNH between 2000-2011. MNH was defined as abnormal NBS followed by TSH between 5-30 mU/L and normal FT4 on confirmatory serum tests. We assessed the clinical course of infants with MNH according the etiology determined by Tc-99m scan. Scan data and clinical course of infants with classic congenital hypothyroidism (CH) were analyzed in parallel.
Results: We identified 69 infants (52% boys) with MNH and 164 infants (34% boys) with classic CH. Tc-99m scan results were divided into 4 subgroups as follows: no uptake in 7% of MNH vs 24% of classic CH ($p< 0.01$), decreased uptake/anatomical abnormalities in 39% vs 46% (p=NS), increased uptake in 35% vs 26% (p=NS), and normal uptake in 19% vs 4% of infants ($p< 0.01$). Among the MNH patients, neither NBS TSH, confirmatory TSH and FT4, mean LT-4 treatment doses, number of dose escalations, nor post-treatment FT4 and TSH differed among the 4 Tc-99m subgroups. In contrast, the clinical features in classic CH differed, as expected, among the subgroups. Among MNH infants, who reached 3 years of-age, trial-off treatment was successful in 6 of 11 (55%) with no difference in success rates among the Tc-99m subgroups.
Conclusions: Clinical data did not differ among Tc-99m-defined etiologies in MNH, and scintigraphy did not predict success of trials off therapy. The clinical utility of information provided by Tc-99m scan during the evaluation of MNH is low; therefore, obtaining these scans in MNH infants may not be an effective use of health care resources.

P2-d3-1165 Thyroid 6

Familial non-autoimmune hyperthyroidism: activating mutation of thyrotropin receptor gene discovered after three generations of a family

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Background: Familial Non-autoimmune hyperthyroidism (FNAH) is a rare aetiology for congenital hyperthyroidism due to activating mutation of thyrotropin receptor (TSHR). Recommended treatment is total ablation of thyroid tissue by total thyroidectomy followed by radioiodine administration.
Objective and hypotheses: To describe a family with three generations of members affected by this condition. Index case was a Chinese girl who had been having hyperthyroidism since seven years old and was treated as Graves' disease. Her course of illness was prolonged and difficult to be controlled with anti-thyroid medication. Her mother also suffered from hyperthyroidism and had undergone two thyroid surgeries. The patient delivered a newborn girl at the age of twenty, who was hyperthyroid since birth and remained so by fifteen months old. Thyroid receptor antibody was found to be negative for the patient and her daughter, and subsequently their blood samples were sent to investigate for mutation in *TSHR* gene.
Methods: DNA were isolated from peripheral blood lymphocytes and all *TSHR* coding exons were amplified, purified and sent for direct DNA sequencing.
Results: The index case and her daughter were heterozygous for p.L629F (TTG>TTC) activating mutation in *TSHR* gene.
Conclusions: Diagnosis of FNAH can sometimes be difficult as similar familial predisposition can also be found in autoimmune hyperthyroidism. Genetic confirmation is important to predict outcome and provide most appropriate treatment.

P2-d3-1166 Thyroid 6

Familial papillary thyroid carcinoma: description of 4 paediatric cases

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Introduction: Familial papillary thyroid carcinoma (FPTC) represents 5% of all Papilar Thyroid Carcinomas and is clinically defined by 2 or more first degree relatives with the tumor, without components of any genetic syndrome. Its inheritance is autosomal dominant with incomplete penetrance.
Objetive: To describe 4 index cases, their clinical features.and variable expressivity.
Cases:
1. Girl with autoimmune thyroiditis; FPTC in maternal family: 1 cousin, 1 aunt and grandgrandfather. At 10y was diagnosed with focal PTC. No local, vascular neither lymph invasion. No recurrence at 1 year follow up.
2. Healthy girl; mother with PTC; at 13y was diagnosed with bilateral PTC, diffuse sclerosing variety. She had local, vascular and lymph invasion. The cancer recurred at 9 months of follow up.
3. Girl with autoimmune thyroiditis. 2 cousins (mother's family) with PTC. At 13.3y was diagnosed with multinodular PTC with local invasion. 4 years of fllow up, without recurrence.

4. Healthy male. Father and 1 aunt with PTC. At 14.5y was diagnosed with focal PTC with lymph metastasis. No recurrence at 4,5 years of follow up.
Discussion: FPTC must be clinically suspected in a multinodular or bilateral lesion, or in children and males cases, although is more common in women 2-3:1. Usually is diagnosed at earlier age than sporadic carcinoma and has a high frequency of local invasion (32%), recurrence (20-50%) and lymph node metastases (57%).
It's associated with benign thyroid disease (36-57%) and increased risk of other neoplasms. It has a worse prognosis than sporadic carcinoma and a high suspect index at the affected families is necessary for a precocious diagnosis and treatment.

P2-d3-1167 Thyroid 6

A novel *MCT8* mutation in a Japanese patient with Allan-Herndon-Dudley syndrome

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Background: Allan-Herndon-Dudley syndrome (AHDS), an X-linked condition, is characterized by severe psychomotor delay, muscle hypoplasia, spastic paraplegia, and athetoid movements, in combination with characteristic thyroid hormone abnormalities. Mutations in the *MCT8* gene coding for the monocarboxylate thyroid hormone transporter 8 have been associated with AHDS.
Patient: This Japanese male patient was born at 41 weeks of gestation after an uncomplicated pregnancy and delivery. His elder brother and father were clinically intact; however, his mother had mild mental retardation. At birth, his length was 52.5 cm (+1.4 SD), his weight 3.8 kg (+1.6 SD), and his head circumference 34.5 cm (+0.6 SD). He was referred to us because of inadequate head control, marked hypotonia, spastic paraplegia, deformed skull and poor weight gain. Thyroid function test demonstrated high serum FT3 (9.22 pg/ml [normal range: 2.0-3.4]), low FT4 (0.64 ng/dl [normal range: 0.9-1.6]), and normal TSH levels (3.29 uU/ml [normal range: 0.40-3.80]). Brain magnetic resonance imaging showed extensive delay in myelination.
Mutation analysis: We performed mutation analysis for *MCT8* in the patient by PCR-direct sequencing and identified a novel missense mutation (p.Gly276Arg, c.826G>A). This substitution was not found in 125 healthy control subjects.
Conclusions: The presence of characteristic alterations in thyroid hormones would be a strong indicator of AHDS and the presence of a *MCT8* mutation could confirm the diagnosis. Although female carriers of *MCT8* mutations typically do not express phenotypic abnormalities, mild mental retardation in the mother implies the existence of unfavorable random X-inactivation.

P2-d3-1168 Thyroid 6

Bone maturation and growth in children with congenital hypothyroidism detected by neonatal screening: a longitudinal study

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Background: Screening program for congenital hypothyroidism (CH) and early start of thyroid hormone replacement allow the affected children to grow up normally. However, there are few studies that evaluate bone maturation.
Objective and hypotheses: To study bone age (BA) and growth in children with CH detected by neonatal screening and the relationship with the severity of the hypothyroidism at diagnosis.
Methods: Eighty three children (M=22, F=61) with CH detected by the Neonatal Screening Program of Buenos Aires Province were followed up longitudinally to the age of 3 years. Median age at diagnosis and start of treatment was 16 days (Mn=6, Mx=30). Levotiroxine treatment started at diagnosis in all cases. Mean initial levotiroxine dose was 13.12 ug/kg/day. Height, weight and BA were evaluated at chronological age: 12, 24 and 36 months (mo). BA was expressed as percentage of bone maturation (%BA) (Tanner and Whitehouse method). All patients were divided in 2 groups: G1 with severe CH (pretreatment T4 level < 3 ug/dl) (n= 42) and G2 with less severe CH (pretreatment T4 level ≥ 3 ug/dl) (n= 41). Statistical analysis: Student t test was used to compare the data with the references and between groups. Pearson correlation coefficient was calculated to evaluate the relationship between %BA and the other variables.
Results: Mean weight and height were normal at all ages. Mean %BA was 104.03% at 12 mo (p=0.013), 108.99% at 24 mo (p< 0.001), and 107.92% at 36 mo (p< 0.001). No significant differences were found between groups. %BA was positively correlated with weight at 24 (r=0.409,p< 0.001) and 36 mo (r=0.295,p=0.007), and height at 24 (r=0.474,p< 0.001) and 36 mo (r=0.382,p< 0.001).
Conclusions: Although bone maturation was within normal limits, a slight advance was observed with respect to chronological age. However, there was no relation with the severity of CH. Further follow-up will be necessary to evaluate how it would impact on final height.

P2-d3-1169 Thyroid 6

Severe acquired primary hypothyroidism in children older than 3 years: a retrospective analysis of 43 cases

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Background: Severe, acquired hypothyroidism in childhood is a rare condition, mostly caused by autoimmune thyroiditis. Concerning its impact on linear growth only inconsistent data based on small patient numbers is available.
Objective: To describe the course of severe acquired hypothyroidism based on a single center patient cohort.
Population and methods: Retrospective analysis of patients diagnosed with severe acquired hypothyroidism from 2004 to 2012. Inclusion criteria: age > 3 years, initial TSH >30 mU/l and reduced T4 or fT4. Exclusion criteria: congenital and drug-induced hypothyroidism. 43 patients were included, mean age 10.75 years (3.3-15.25), 88% girls and 12% boys.
Results: 99 patients were selected by TSH > 30 mU/l and age >3 years, 43 were included by meeting all criteria. Presenting symptoms: goiter (26%), tiredness (23%), weight gain (19%), growth retardation (19%). Random diagnosis by blood test 26%. TSH was elevated (median 100 mU/l [0.3-4 mU/l]), fT4 (median 3,55 pg/ml [8-19 pg/ml]) and T4 (median 2,85 µg/dl [5.3-11 µg/dl]) was low. Thyroid autoantibody were detected in 93% (anti-TG-ab 70%, anti-TPO-ab 93%,), 7% had no antibodies. Abnormal sonography was found in 95%, goiter in 63%. 59% were prepubertal at diagnosis. Most patients had mild growth retardation (median height SDS -0.58), 14% were short (height SDS < -2) at diagnosis. Height SDS at diagnosis was significantly correlated with fT4 (r=0,477, p= 0,16). Catch-up growth was not correlated with fT4. Follow-up showed complete catch-up growth in 43%; which was more frequent in prepubertal (70%) than in pubertal (30%) children. Complete remission was found in 5%.
Conclusions: All severe acquired hypothyroidisms were caused by autoimmune thyroiditis. Although T4 was low, 26% of patients were not diagnosed clinically. Despite adequate therapy not all children experienced complete catch-up growth. Pubertal status seems to be more important for catch-up growth than initial fT4.

P2-d3-1170 Thyroid 6

Ovarian and thyroid disorders in a group of adolescents with type 1 diabetes

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Background: Diabetes mellitus is a widespread disease all over the world, associated to ovarian failure and hypogonadism of autoimmune disorders in women with type 1 diabetes mellitus.
Objective and hypotheses: Evaluating the incidence of ovarian and thyroid functional disturbances in a group of teenagers with diabetes mellitus.
Methods: We studied a group of 38 patients, age between 14-18 years, with diabetes mellitus type 1 (IDDM), diagnosed at least 5 years, compared to a witness group (74 teenagers) without disturbances of glycemia. There were appreciated: characteristics of menstrual cycle, development of sexual characteristics, blood level of ovarian hormones and gonadotropes, thyroid and mammary modifications observed by clinic examination and ultrasonography, as well as the measurement of free thyroxine (F-T4), thyrotropine (TSH) and antimicrosomal antibodies (ATPO).
Results: Menstrual disturbances were observed in 77.4% of the diabetic patients, compared to 24.4% of the patients from the witness group. Breast development was normal in 86.1% of the patients in the witness group and only 35.4% in the diabetic patients. Modifications of the blood levels of the ovarian hormones were significantly present in the diabetic patients (77.4%). Mammary pathology fibrocystic pattern was present in both groups in low percentage without statistical significance. The incidence of goiter, its degree of development and thyroid volume were higher in the diabetic patients. Functional thyroid disturbances were seen in 4 patients with diabetes; 3 cases with subclinic hypothyroidism and 1 case with clinically manifested hypothyroidism. The presence of thyroid antibodies was seen in 29% of the diabetic teenagers compared ti 2.4% of the teenagers from the witness group.
Conclusions: For the patients with diabetes there exists a significant risk for the ovarian functional disturbances, sexual disturbances, thyroid autoimmunity and mammary and thyroid structural lesions.

P2-d1-1171 Thyroid 7

Familial dysalbuminemic hyperthyroxinemia (FDH): a reminder to take extended family histories

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Background: FDH rare but the commonest inherited cause of euthyroid hyperthyroxinemia in Caucasians. Variant serum albumin with increased T4 affinity results from mutations in the albumin gene (R218H most Caucasians; R218P Swiss & Japanese). Failure to recognise it may lead to inappropriate tests or treatment and has no known long term medical consequence. Immunoassays vary in their response to the anomaly, yielding aberrant results. Diagnosis has been simplified with molecular tests.
Objective and hypotheses: Case reports of a Turkish family.
Methods: Case Study
Results:
Case 1: Index pt TeB 14 yr boy complaining of exertional chest pain, breathless, tired and episodes of nausea, sweating and pallor. Clinically euthyroid, no goitre. Local lab: *Centaur* assay: TSH 2.7(0.3-5.5)mIU/L; FT4 25(9-25) pmol/L, FT3 8.4(3.5-6.5)pmol/L. TPOAbs NEG; 24h urine CATs normal excluded phaeochr. ECG/CXR: normal. *FH*: Mother - AI hypothyroid on L-T4. Sisters / father investigated as below, hence referral of *Case 1* to specialist unit involved.
Case 2: Sister LiB, 20yrs investigated for sweat/tachycardia/tiredness. Local lab *Roche* assay: TSH 1.6, FT4 32.1, FT3 6.3: prompted repeat with DELFIA assay: TSH 3.5, FT4 19.1, FT3 7.3, TT4 259(69-141), TBG 17(14-31). Results suggested FDH, hence check Father and twin sister (Case 3).
Case 3: LeB, 20 yrs: asymptomatic. Local lab *Roche* assay: TSH 1.6, FT4 25.5, FT3 5.5. DELFIA: TSH 1.8, FT4 18, FT3 6, TT4 284, TBG 25.
Case 4: Father RB, Local lab *Roche* assay: TSH 1.6, FT4 25.5, FT3 5.5; DELFIA: TSH 1.3, FT4 19.0, FT3 6.3, TT4 248, TBG 16.
DNA tests identified R218H mutation in Cases 1-4.
Index patient's symptoms resolved with time and Omeprazole.
Conclusions: A non-suppressed TSH in the presence of raised fT4 / fT3 should always trigger suspicion of non-thyroidal disorder and further investigation. A strong family history of abnormal thyroid function tests should prompt consideration of genetic disorders previously unrecognised within that family.

P2-d1-1172 Thyroid 7

A case of MCT8 deficiency with a novel mutation in the *SLC16A2* gene

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Introduction: Monocarboxylate transporter 8 (MCT8) is a potent thyroid hormone transporter which facilitates T3 uptake into central neurons. In patients with mutations in the MCT8 gene, thyroid function tests show elevated FT3, lowered FT4 and normal or moderately elevated TSH levels in the blood. This disorder is characterized by X-linked mental retardation, reduced muscle mass, hypotonia, quadriplegia or spastic paraplegia. We recently experienced a male case of MCT8 deficiency with a novel mutation in the *SLC16A2* gene, and performed endocrinological investigations for him.
Case study: The patient is an 8-year-old boy. Pregnancy and delivery were uneventful. There was family history of disorders in neurological development. At age 4 months, poor weight gain and hypotonia with poor head control were pointed out, and blood tests showed elevation of lactic acid. Brain MRI demonstrated delay of myelination at age 1 year. At present, mental retardation, poor head control, reduced muscle mass, hypotonia and short stature are found. On current thyroid function tests, serum levels of TSH, FT3 and FT4 were 2.44 mIU/ml, 4.2 pg/ml and 0.6 ng/dl, respectively. *SLC16A2* gene analysis was performed for the patient, because his clinical findings suggested MCT8 deficiency. A novel missense hemizygous mutation (p.R445S) was identified in exon 4. This mutation was also found in one allele of his mother. Thyroid function tests showed the typical pattern for MCT8 deficiency at age 8 years. However, euthyroid was detected in early childhood. On TRH test, the primary hypothyroid pattern of TSH was recognized. Brain MRI and cervical echogram demonstrated atrophy of pituitary and thyroid glands.
Conclusion: Our findings suggest that thyroid status of MCT8 deficiency might be changeable according as the time of examination, and therefore regular thyroid function tests are necessary. Additionally, we should evaluate the pituitary function and the size of thyroid gland in MCT8 deficiency.

P2-d1-1173 Thyroid 7

Thyroid nodules in paediatrics: a 4-year prospective study

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Introduction: Pediatric thyroid nodules have a greater risk of malignancy than in adults.
Objective and hypotheses: To study a pediatric cohort of patients with thyroid nodules.
Methods: We prospectively studied 66 consecutive patients referred to our center between 2007 and 2011. Clinical features, thyroid function, Doppler ultrasound (US), ^{99m}Tc scan, US guided FNAB, cytology categorized according to the Bethesda System for Reporting Thyroid Cytopathology and histol-

ogy of those patients who underwent surgery were evaluated. Also differences between benign and malignant nodules were characterized.
Results: 59 patients were analyzed (7 lost to follow up) 83% girls, median age 13,9 years. 88% pubertal. Cause of referral: palpable nodule (78%), multinodular goiter (MNG) (13,5%), goiter (5%) and US finding (3,4%), 5 % had risk factors. 86,7% were euthyroid, 8,9% hypothyroid and 4,4% hyperthyroid. 22,2% had positive antithyroid antibodies. Median US greatest nodular diameter was 21mm (r:8-80), 63% were solid, 19% had central microcalcifications, 5% undefined limits, 22% central vascularization and 8% pathologic lymphadenopathies. 62% were cold. FNAB diagnostic performance (excluding 15,9% nondiagnostic samples) showed a 67% sensitivity, 93% specificity, 67% PPV and 90% NPV (diagnostic efficiency 86%). 45 patients underwent surgery: 10 papillary carcinoma, 35 benign. Global malignancy rate was 22%. Papillary carcinoma was found in 38,5% of MNG and 15,6% of solitary nodules. All carcinomas were euthyroid, solid on US ($p< 0,05$) and 50% presented pathologic lymphadenopathies ($p< 0,05$). Malignant results in FNAB were always cancer. Malignancy rates for each cytology subtype were: I 28,6%, II 8,7%, III 16,7%, IV and V 0% and VI 100%.
Conclusions: Our findings confirm that most pediatric nodular disease is benign, however with a greater incidence of cancer that usually reported in adults. US and US guided FNAB were the most useful tools in our strategic approach.

P2-d1-1174 Thyroid 7

Extra-thyroid congenital abnormalities with thyroid dysgenesis

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Background: The higher frequency of extra-thyroidal congenital malformations (ETCM) has been reported in children with congenital hypothyroidism (CH) compare with general population. Congenital cardiac malformation (CCM) is higher among children with thyroid dysgenesis (TD) however CCM prevalence is %0.08, and the most common defect is VSD in normal population
Objective and hypotheses: To investigate the frequency and type of additional ETCM in children with thyroid dysgenesis among from congenital hypothyroid patients have born between 1991-2012.
Methods: We include 41 children with confirmed primary CH due to TD and excluded the patients with Down syndrome. They were 27 girls. Diagnosis ages ranged from 4 days to 4 years. The etiology of TD was determined with thyroid ultrasound and scintigraphy. Malformations were identified by physical examination, echocardiography, abdominal/ renal ultrasound and x-ray.
Results: Twenty seven of 41 patients had ectopic thyroid (%66), 12 had thyroid agenesis (%29) and 2 had hemiagenesis (%5). High ratio of ETCM (% 48 n20) was observed. Nine patients had more than one system malformations. The most frequent malformation was CCM (%22 n9) such as: ASD (n6), MI (n2), PS (n1). Seven patients had skeletal abnormalities (%17) such as; developmental dysplasia of hip (n3), poli/syndactyly (n3), pes planus (n1) and pectus excavatus (n1). Two patients had ophalmologic abnormalities; strabismus and synkinesia. Two patients had urogenital malformations; horse shore kidneys and testicular atrophy. Nine of patients had dysmorphic facial features and one of them diagnosed as Towsen Brock Syndrome.
Conclusions: We observed that the most common type of malformation was ASD. The high rate of CCM among with TD suggest that the possible genetic links both thyroid gland and cardiac development during embriogenesis. we recommend to investigate other abnormalities in children with CH and perform echocardiography for all patients with TD during infancy.

P2-d1-1175 Thyroid 7

Review of presentation and management of juvenile thyrotoxicosis at a single centre between 2000-2010

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Background: Juvenile thyrotoxicosis is treated with anti-thyroid drugs using block-and-replace or dose-titration regimen. There is a high rate of relapse and many patients require definitive treatment with surgical or radio-iodine ablation. Increasingly radio-iodine therapy is being used in children, particularly in the United States, but experience with this is limited in the UK. In our unit, surgery is performed by our experienced Paediatric thyroid surgeon along with his adult counterpart, in children who relapse after medical treatment.
Aims: To review presentation, management and outcome of juvenile thyrotoxicosis at Leeds Children's Hospital, Leeds, UK.
Methods: Case notes review of all children aged 0-18 years diagnosed with thyrotoxicosis between January 2000- December 2010.
Results:
Presentation: Twelve eligible patients were identified. This gives an incidence of 0.7/100,000/ year. Figures may be higher due to difficulties in ascertainment. All patients were female aged 10-18 years with a median peak at 14.4 years and they all presented with classical symptoms of thyrotoxicosis.
Treatment: All patients were treated with carbimazole. Block and replace regimen was used in 10 (83%) patients and dose titration in 2 (17%). Total duration of treatment varied from 9 months to 5 years.
Outcome: One patient is still on medical treatment after 4 years. Six (55%) patients had surgery due to goiter or difficult symptom control with anti-thyroid drugs and 5 (45%) were treated medically. In medically treated patients, 3 (60%) relapsed on stopping treatment and 2 (40%) went into remission after 1-2 years of treatment . All 3 relapsed patients underwent surgery.
Conclusion: Our findings of presentation and relapse of juvenile thyrotoxicosis are consistent with figures reported in the literature. In view of the high relapse rate and the developing experience of radio-iodine ablation, definitive treatment may need to be considered earlier in our group of children.

P2-d1-1176 Thyroid 7

An adolescent girl with hypothyroid coma due to autoimmune thyroiditis

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Background: Profound hypothyroidism leading to coma has not been reported in adolescents.
Case presentation: A 13-year-old adolescent girl presented with coma. Mother reported fatigue, increased sleepiness, and deterioration of school performance, apathy, secondary amenorrhea, change in voice, and weight gain for 5 months. No history of dyspnea, palpitations or chest pain, drug intake, trauma, or any systemic illness. No family history of endocrine disorders was reported. Mother reported that the girl lost consciousness after 30 minutes of feeling dizzy.
Results: She had hypothermia (36 C), hypotension (BP = 90/ 55 mmHg) , and bradycardia (50/min). She was comatosed (GCS = 8/15) with periorbital edema, loss of the lateral eyebrows, dry skin, and large smooth symmetrical firm (40 gram) goiter. Her TSH = 417 mU/L and FT4 of 1.7 pmol/L (normal 11-19 pmol/L) and antimicosomal antibody (AMA) titer of 1:1,800 confirmed the presence of severe hypothyroidism due to autoimmune thyroiditis. Thyroid ultrasonography revealed bilaterally enlarged thyroid lobes with heterogenous echopattern and multiple nodules. MRI of the sella turcica revealed global diffuse enlargement of the pituitary. She received intravenous T3 therapy that regained her consciousness in 10 hours, followed by intake of l-thyroxine 100 microgram daily. Vigor returned and voice improved within 2 weeks. FT4 and TSH were normalized in 4 weeks. Pituitary size was normalized in the follow up MRI after 6 months.
Conclusions: This case raises the awareness of physicians to include hypothyroid in the differential diagnosis of coma in this age group.

P2-d1-1177 Thyroid 7

Partial pituitary thyroid hormone resistance in a 14-year-old boy: a case report

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Background: The thyroid hormone resistance syndromes are disorders in which the body's tissues are resistant to the effects of thyroid hormone.In most cases caused by mutation in the thyroid hormone receptor beta gene. Clinically characterized by hyperthyroidism, hypothyroidism or euthyroidism depending on subtype of disorder- generalized, selective peripheral or selective pituitary resistance.
Objective and hypotheses: We described male patient with permanent tachycardia during last several years.
Methods: A boy 14.2 years old, height -174cm (+1.2SD), m=53kg, BMI=17.3 (< 50th percentile), puberty Tanner 3.
Complaints: Tachycardia 90-130 per minute at rest for several years, lability of mood, sweating. Heart rate -102\min, BP - 125\70 mmHg.
Skin is damp and clean. Thyroid gland is palpatory enlarged. Ophthalmic symptoms are negative. Family history: mother suffer from autoimmune thyroiditis with hypothyroidism.
Previous investigations: ECG: sinus tachycardia. deviation of the electrical axis to the left.
TSH - 3.5 IU\l (0.4-4.0), 2009; TSH - 2.8 IU\l (0.4-4.0), 2011
Re-examination: US: thyroid gland is enlarged - Vd-6,5sm3, VS-6.7sm3. Structure is homogeneous, echogenicity of normal tissue, no additional tumors.
TSH - 3.7IU\l (0.4-4.0) ;fT4 - 25 pmol\l(9-19);fT3 - 6.1 pkg\ml(1.7-3.7);T4 - 183 nmol\l (55-170);ATPO - negative;At-TG - 10 IU\ml (< 60)
Braine MRI witch contrast: didn't found any pathological changes.
Results: Patient was administered beta-blockers (propronalol) 30mg\day. 6weeks after treatment start:
TSH - 3.3IU\l (0.4-4.0);fT4 - 22.5 pmol\l(9-19);fT3 - 4.8 pkg\ml(1.7-3.7)
Heart rate ranges between 80-100\min at rest.There are decreased the clinical symptoms of hyperthyroidism.Genetic test has been recommended.
Conclusions: Normal TSH level doesn't exclude hyperthyroidism.Syndromes of thyroid hormone resistance are rare in practice and can be missed despite of thyroid dysfunction clinical pattern.

P2-d1-1178 Thyroid 7

Amiodarone-induced thyrotoxicosis: a rare complication in children

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Background: Amiodarone (AM) is useful as pediatric effective anti-arrhythmic treatment and amiodarone-induced-hypothyroidism has been frequently reported. Conversely, amiodarone-induced thyrotoxicosis (AIT) has been rarely reported in children. In adults, the AIT treatment is complicated according to the two different types of AIT: type 1, iodine-induced hyperthyroidism type and type 2, a drug-induced destructive thyroiditis.
Objective: The objective of the retrospective study was to screen AIT from French pediatrics endocrinology centers and to evaluate the treatment.
Patients: We screened AIT from French society of pediatric endocrinology and diabetologia. Only five patients have been reported: 3 with type 2 AIT, one with type 1 AIT and one with a "mixed" form of AIT.
Results: Patients received on average 31 months of AM (range:[11 months-72 months]). AIT was developed 9 months after the cessation of the AM in the patient with AIT type 1 or during the treatment by AM (n= 3 / 4 patients with type 2 AIT). AM was discontinued. Four patients received carbimazole which restored normal thyroid function in 3 months in patient with type 1 AIT, but was ineffective after 2 months in all patients with AIT 2. Glucocorticoid were effective in all the patients with type 2 AIT (mean: 10 weeks of treatment)
Conclusions: The incidence of AIT may be lower in children than adults. The distinction between the 2 types of AIT is required to choose the appropriate treatment.

P2-d1-1179 Thyroid 7

Prevalence of permanent congenital hypothyroidism

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Background: Congenital hypothyroidism (CH) considered as one of the preventable causes of mental retardation in infants. Neonatal screening for CH has been developed in many countries in order to early diagnosis and treatment of CH and consequently preventing its related neurodevelopmental complication. Evidences suggested that the world wide incidence of CH has been increased recently due to reasons such as improved protocol of CH screening, increased detection of transient form of the disease and environmental factors.
Objective and hypothesis: Considering that the main recourses allocation for CH in a community is designed according to the rate of its permanent forms and the importance to determine the reasons for the higher occurrence of CH in Iran, in this study we report the prevalence of permanent CH(PCH) in Isfahan province seven years after initiation of the program in Isfahan**.**
Methods: In this cross-sectional study, children with primary diagnosis of CH studied. They clinically examined and their medical files were reviewed by a pediatric endocrinologist .Considering screening and follow up lab data, radiologic findings and the decision of paediatric endocrinologists the final diagnosis of permanent CH(PCH) was determined.
Results: In this study 464648 neonates screened in Isfahan province. The coverage percent of the CH screening was 98.9%. The rate of recall was 2.1%. 1990 Neonates were diagnosed with primary CH. PCH was diagnosed in 410 neonates. The prevalence of PCH and Transient CH(TCH) was 1 in 1133 and 1 in 294live births. The most common etiology of CH was thyroid dyshormonogenesis.
Conclusions: It is suggested that though the prevalence of PCH is high but the higher prevalence of CH in Isfahan is commonly due to cases with TCH. It is recommended to study the reasons of higher rate of TCH and different etiology of PCH in our community.

P2-d1-1180 Thyroid 7

The role of thyroid ultrasonography in the etiological investigation of patients with congenital hypothyroidism

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Background: Thyroid ultrasonography (T-US) can help the etiologic diagnosis of congenital hypothyroidism (CH). Dysgenesis includes athyreosis, ectopia and thyroid hypoplasia. Normal-sized or enlarged topic thyroid suggests dyshormoniogenesis.
Objective and hypotheses: To describe T-US findings and their contribution in the CH etiologic diagnosis.
Methods: Thirty-five patients with CH were summoned; 31 (18 females,13 males) attended and agreed to undrego a new T-US, aged 2 to 45 years (median: 8). All of them had been treated with L-thyroxine, and some had previously started etiologic research including ^{131}I thyroid scanning (T-S) (n:13) and T-US (n:24) around 3-4 years.
Results: According to the current T-US, 8 patients (25.8%) had ectopic thyroid and 23(74.2%) topical, with volume ranging between 0.2 to 14.2 mL (median: 2mL). Among these, 11 were hypoplastic (0.2 to 1.5 mL), and 12 had thyroid volume between 2 and 14mL. T-S showed 100% of concordance

with current T-US although allowing perchlorate test performance (n:11), disclosing 3 cases of iodide organification defect. Comparison between twenty-four T-US performed previously with current ones showed thyroid volume reduction in 7, probably due to treatment. So the diagnosis of hypoplasia must be done in the neonatal period, before L-thyroxine treatment.
Conclusions: T-US and T-S are the imaging modalities of choice in the evaluation of thyroid in CH. They are comparable but T-US can be done in the neonatal period. In the future, the precise etiologic diagnosis of CH would be performed by molecular study and T-US could guide the early evaluation with no need for L-thyroxine interruption.

P2-d1-1181 Thyroid 7

Juvenile hyperthyroidism

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Background: Hyperthyroidism is less frequent in children than adults, and its clinical profile is different.
Objective and hypotheses: Our study was to analyze the clinical characteristics of hyperthyroidism in children and adolescents.
Methods: It is a retrospective study concerning 161 patients (129F/32M) with mean age of 15.63 ± 3.51 years, their medical records were reviewed.
Results: 98.1 % of patients have Graves' disease; appealing symptoms were thyrotoxicosis signs in 69 %, ophtalmological signs in 15 % and goiter in 16 %; diagnosis delay was of 20.73 ± 20.69 months; clinical picture was obvious in 81 % and discrete in 19 %; goiter was of type II/type III in 74 % and of type I in 26 %; exophtalmous was present in 69 % and it was severe in 12.5 %; several complications were recorded: cardiothyreosis (1.86%), dysglycémie (13.04%), myopathy (3.72%) and behavioral disorders (6.83%).
Conclusions: Graves' disease is the main etiology of hyperthyroidism in children; the diagnosis is often delayed although it is clinically obvious so complications may occur, therefore hyperthyroidism should be diagnosed and treated promptly.

P2-d1-1182 Thyroid 7

Newborn screening program for congenital hypothyroidism in Montenegro

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Background: Neonatal screening is a medical procedure in the context preventive medicine aimed at early identification of infants affected by certain disease. Early diagnosis and treatment of congenital hypothyroidism (CH) are crucial to the prevention of severe intellectual deficit. It has been 6 years since newborn screening started in Montenegro in 2007.
Objectives: The aim of this study was to assess the incidence of CH over the last 5 years and analyze and summarize the status of newborn screening in Montenegro.
Methods: This is a population-based retrospective study. Blood samples were collected from the heels of newborns 72 hours after birth and thyroid-stimulating hormone (TSH) was detected. Dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA) was used for detection.
Results: Over the period January 2008 - December 2012, 40758 newborns were screened and 17 cases were confirmed as CH. Screening rate were 100%. The catt -of value in our laboratory was 10 mU/L. Recall rate was 0.97-1.36%.
Conclusion: This is the first report about newborn screening for congenital hypothyroidism in Montenegro.During the period of analysis an incidence rate of 1:2264 was calculated.

P2-d2-1183 Thyroid 8

A study of iodine organification in transient hypothyroidism with biallelic *DUOX2* mutations: organification defect is not an invariable feature

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Background: Dual oxidase 2 (DUOX2) is a complex components of thyroglobulin iodination, and inactivation mutations may lead to thyroid dyshormonogenesis due to the iodine organification defect. It has been reported that a portion of biallelic *DUOX2* mutations causes transient hypothyroidism (TH), however their iodine organification status has not been established.
Objective: We examined iodine organification in biallelic *DUOX2* mutation-carrying patients diagnosed in our TH cohort study.
Methods: The subjects were three unrelated TH patients that had biallelic *DUOX2* mutations. A perchlorate discharge test was performed in each case to evaluate thyroid iodine organification status.
Results: Their thyroid function tests, radioactive iodine uptake and perchlorate discharge rate are shown in Table 1. Iodine organification faculty was normal with all three patients.

	Case 1	Case 2	Case 3
Age/Sex	17/M	6/F	6/F
DUOX2 genotype	H678R/S965L	K530X+H678R/K628RfsX11	G624AfsX15/R1110Q
Thyroid function tests during levothyroxine discontinuation	TSH 3.5 mIU/L, FT4 1.3 ng/dL	TSH 2.3 mIU/L, FT4 1.9 ng/dL	TSH 5.1 mIU/L, FT4 1.9 ng/dL
Radioactive iodine uptake at 24 hours	26.9 %	18.9 %	52.2 %
Perchlorate discharge rate	0 %	0 %	0 %

[Table1]

Conclusions: Elevated perchlorate discharge rate dose not seem an invariable feature of *DUOX2* mutation carriers, although most previous cases had positive results. The phenotypic spectrum of biallelic *DUOX2* mutations is broader than currently accepted.

P2-d2-1184 Thyroid 8

Thyrotoxic hypokalaemic periodic paralysis in a Hispanic teenager

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Introduction: Thyrotoxic hypokalemic periodic paralysis (THPP) is a rare complication of hyperthyroidism presenting with hypokalemia and acute body paralysis. We report the case of a Hispanic teenager with a known history of hyperthyroidism, who presented to the Emergency Department with palpitations and proximal muscle weakness.
Case study: The 15 year-old Hispanic female presented with palpitations and profound extremity weakness. She was being treated with methimazole and propranolol at home. The weakness began 6 days prior and worsened until she was unable to stand and walk. She had a sore throat, fever, headache, and diarrhea. She appeared jittery and had a goiter, resting tremor, and proptosis. She was tachycardic (110bpm) and hypertensive (163/63mmHg). She had weakness and 4/5 strength in upper and lower extremities bilaterally. Her laboratory workup revealed a TSH of < 0.01 (range 0.5-4.5mIU/L), FT4 of 4.9ng/DL (range 0.8-1.7ng/DL), and FT3 of 1258pg/DL (range 230-240pg/DL). Potassium was 3.2mm/L, and sodium was 130mm/L. She was started on oral

potassium 20mEq daily and intravenous maintenance fluids with 20mEq KCl. She was restarted on propranolol and methimazole. Her symptoms improved slowly over two days. Follow up laboratory workup revealed potassium and sodium levels of 3.4mm/L and 135mm/L, respectively. She was discharged on metoprolol, methimazole, and oral potassium daily.
Conclusion: Our patient's case is consistent with previous cases of THPP in her signs, symptoms, and hypokalemia. However, to date, no cases of THPP have been described in teenage girls, particularly of non-Asian descent. Prompt diagnosis, monitoring, and management with potassium supplements, b-blockers, and antithyroid medications alleviates symptoms and may prevent cardiac complications and recurrences of paralysis. While THPP tends to occur in older males of Asian descent, it must be ruled out in all patients presenting with hyperthyroidism, paralysis, and hypokalemia.

P2-d2-1185 Thyroid 8

Thyroid function abnormalities in term newborns from Korean mothers with autoimmune thyroid disease

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Background: Maternal autoimmune thyroid disease(AITD) may affect neonates thyroid function.
Objective and hypotheses: To evaluate of thyroid function status in term newborns of mothers with autoimmune thyroid diseases retrospectively.
Methods: Sixty-five term neonates born from 63 mothers with Hashimoto's disease(57) or Graves' disease(8) had a thyroid function test by measurement of serum thyroid stimulating hormone(TSH) and free thyroxine(FT4) between 3rd and 5th day of life. TSH receptor antibodies, thyroid peroxidase antibody, and antithyroglobulin antibodies were also measured.
Results: A total of 52.3% (34) of neonates (87.5% of neonates from Graves' disease mothers and 47.4% of neonates from Hashimoto's disease mothers.) revealed abnormal thyroid function tests; both increased TSH and decreased FT4 in two neonates and only decreased FT4 in thirty two. Neonate's thyroid antibodies were not related with abnormal thyroid function results; for TSH receptor antibody, thyroid peroxidase antibody,and antithyroglobulin antibody, statistical significance using Student's t-test were p=0.149, 0.25, and 0.308, respectively.
Conclusions: Abnormal thyroid functions were common in early period of time of term newborns from mothers with AITD. Further studies about the change of thyroid function in a later period are needed.

P2-d2-1186 Thyroid 8

Two novel mutations of the *MCT8* gene: clinical and laboratory aspects

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Background: The monocarboxylate transporter 8 (MCT8) is a transporter highly specific for thyroid hormone (TH) present in different tissues, with an important role in central nervous system (CNS). The inactivating mutations of *MCT8* have X-linked inheritance and present clinically with severe cognitive deficiency and hypotonia.
Objective: To describe two male patients with *MCT8* mutation.
Methods: Two male patients evaluated for neurological delay and hypotonia associated to an abnormal thyroid profile.
Results: Laboratory evaluation in plasma showed: elevated concentrations of T3; total and free T4 in the lower limit of normal; and TSH mildly increased. The molecular study identified the following inactivating mutations of *MCT8*, both not previously described: 630insG in exon 1 and p.S561del in exon 6. In the first years of life the weight gain was severely compromised in both patients (weight-SDS: -1.8 and -3.2), while the growth rate was normal.
Conclusions: The clinical picture of our patients suggests that MCT8 is essential for the action of TH in CNS, while tissues less dependent of MCT8 (adipose tissue and bone) suffer the consequences of being exposed to high T3 concentrations. The cases described emphasize the importance of the evaluation of plasma T3 in male patients with neurological delay, allowing rational selection of patients in whom the *MCT8* mutations should be searched.

P2-d2-1187 Thyroid 8

Continuum of phenotypes in the evaluation of hyperthyroidism in children and adolescents with autoimmune thyroid disease referred to a tertiary care centre: Hashitoxicosis versus Graves disease

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Background: The transient hyperthyroid phase of Hashimoto thyroiditis(HT) is known as hashitoxicosis(Htx).It has been reported as second to Graves disease(GD) as the most common cause of pediatric hyperthyroidism.
Objective: To compare the initial laboratory and clinical findings in children and adolescents with GD and Htx referred to our clinic. transient hyperthyroid phase of Hashimoto thyroiditis(HT) is known as hashitoxicosis(Htx).It has been reported as second to Graves disease(GD)as the most common cause of pediatric hyperthyroidism.
Methods: Medical records of 70 consecutive patients (15 M) aged 11.9 ± 3.7 yr (range1.8yr-18.3yr)were reviewed. Demographic, clinical, anthropometric, laboratory, thyroid ultrasound data(Mean thyroid volume per body surface area(MTV/BSA) and echogenicity),time to remission(normalized FT4,T3 and TSH levels) and relapse (clinical findings and thyroid panel) were recorded.
Results: The median follow-up period was34 mo(range13-136mo).SDS of weight and BMI were significantly below the mean(p=0.002).Twenty-two(31.4%)patients were prepubertal. Three patients had ophtalmopathy. Anti-TPO was elevated in82%and anti-Tg was elevated in77%of the whole cohort.TRAB was positive in 20patients with GD by definition.Median remission time was7mo(range1-66 mo). When the initial data of patients with Htx and GD were compared, GD patients had higherFT4(p=0.028),MTV/BSA(p=0.011)and remission time(p=0.007)than Htx patients.Four patients with Htx became TRAB positive and were diagnosed with GD(range: 4-62 mo).
Conclusions: Although timely diagnosis and medical interventions may have hindered the emergence of significant differences between patients presenting at extremes in our cohort, Our findings suggest a continuum of phenotype in pediatric autoimmune hyperthyroidism supporting the need for individualized follow-up schedules independent of TRAB status. Rarity of ophtalmopathy in pediatric GD poses additional diagnostic challenge.

P2-d2-1188 Thyroid 8

Maternal thyroid function during early pregnancy and neurodevelopmental outcome at 6 years

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Background: Thyroid hormones are essential for neurodevelopment from early pregnancy onward. Yet the association between maternal thyroid function in early pregnancy and children's neurodevelopment are sparse.
Objective: Our objective was to study associations of maternal thyroid function of early pregnancy across neurodevelopment of children at age of 6.
Methods: We conducted cohort study of mothers who have thyroid dysfunction at early pregnancy and their children. Some of them were evaluated fetal thyroid size by ultrasonography. Children 's thyroid function and development were checked at cord blood, age of one month, 3 months, 6 months, 1 year, 2 years, 3 years and 6 years. At 6 years, their neurodevelopmental outcome was evaluated by WISCIV or other batteries.
Results: In 82 children whose were recruited at age of one month, 23 (28%)

were followed until age of 6 year. The thyroid dysfunction of mothers contained 7 of Grave's disease, 1 of transient hyperthyroidism in early pregnancy, 7 of Hashimoto disease and 8 of autoantibody-negative hypothyroidism. Their TSH and LT4 levels in early pregnancy were less than 0.01 to 9.83 µU/ml and 0.92 to 2.09 ng/ml. Of 23 children, 3 were treated with L-thyroxin because of mild elevation of TSH with normal FT4. One child out of 11 who performed fetal thyroid ultrasonography had goitor and accelerated heart rate had treated with iodine during pregnancy. The mean of total IQ was 107.4 and all of them in normal range (82 to 127). There is no linear association with maternal TSH (P=0.08), FT4 (P=0.36) and total IQ at 6 years, respectively. One child was pointed out low score (79) in working memory in spite of normal total IQ (91) by WISC IV although her thyroid function had been normal until 6 year of age and her mother was euthyroid with antithyroid antibody was positive during pregnancy.
Conclusions: Maternal thyroid dysfunction with normal FT4 is not a risk factor for neurodevelopment in children at age of 6.

P2-d2-1189 Thyroid 8

Primary cutaneous amyloidosis in an adolescent with Graves disease: previously unknown association

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Background: Extrathyroidal manifestation of Graves' disease are well known presenting as pretibial myxedema, occurring in arms, shoulders, neck, and upper back. Other manifestations include hyperpigmentation, yellowing, and possibly disfiguration of the nails. Amyloidosis is a collective term used for a group of uncommon metabolic disorders, where mucocutaneous manifestations are observed, in both, the non systemic and systemic types. We would like to report a adolescent patient with Grave's Disease presenting of Primary cutaneous amyloidosis (PCA), a previously unknown association.
A 15year old Asian girl diagnosed with Graves disease since 8years, treated with carbimazole and radioactive iodine, is currently in remission. She developed hyperpigmented patches over her arms and back, with no signs of inflammation or infection. The initial investigations, including thyroid function test, ANA, coagulation screen, Von Willibrand factor and short synacthen test, were normal. The skin biopsy revealed evidence of subtle interface dermatitis with post-inflammatory pigmentation, mild increase in papillary dermal mucin, positive amyloid P stain suggestive of PCA.
Primary cutaneous amyloidosis (PCA) is the deposition of amyloid limited to the skin, and not associated with underlying systemic illness. The skin lesions are persistent, usually pruritic and respond poorly to conventional treatment. Three variants of PCA are described; lichen amyloidosis(commonest), macular amyloidosis and nodular amyloidosis(rare).
Association of Primary cutaneous amyloidosis (PCA) has been reported to occur in multiple endocrine neoplasia type 2A. However, there is no reported association of PCA with Grave's disease.

P2-d2-1190 Thyroid 8

Blood coagulation and fibrinolytic activity in children with subclinical hypothyroidism

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Background: Abnormalities of coagulation and fibrinolysis may occur in patients with thyroid disease ranging from subclinical laboratory abnormalities to haemorrahages or thromboembolic events. The influence of subclinical hypothyroidism (SH) on haemostasis is controversial, both hypercoagulable and hypocoagulable states have been reported.
Objective and hypotheses: To investigate the markers of coagulation and fibrinolysis in children with SH.
Methods: Prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, factors V, VII, VIII activities, antithrombin III (ATII), protein C, protein S, Tissue plasminogen activator (PAI1) were investigated in 20 children (10 males), with untreated SH (aged 4-18 years), and in 20 euthyroid controls age and sex-matched. Duration of SH ranged from 0.5 to 8 years.
Results: Serum TSH levels were significantly higher in SH children (6,1±1.6 mU/l) compared to controls (2.5±0.8 mU/l, p< 0,0001), while serum FT4 were comparable (1.5±0.7 vs 1.3±0.1 ng/dl, respectively). No differences were observed between SH children and controls in AT (98,1±11,5 vs 92,2±10,5%) and aPTT (31,6±5,5 vs 32,7±4.6 sec) No differences were observed in other coagulation/fibrinolysis parameters between SH children and controls (table). No correlation was observed between duration of SH and coagulation/fibrinolysis parameters.

	SH children	Controls	p
PC %	96,3±16,9	100,4±19,9	NS
PS %	99,4±23,7	98,7±23,9	NS
Fibrinogen mg/dl	301,2±48,0	299,3±83,1	NS
FV %	102,2±37,1	91,9±21,7	NS
FVII%	102,1 ±17,1	89,1±20,4	NS
FVIII%	88,3±35,3	92,5±28,1	NS
ATIII%	104,7±6,7	105,6±8,1	NS
PAI1 UI/mL	2,3±1,2	1,8±0,9	NS

[Table]

Conclusions: Persistent SH in children is not associated with abnormalities in coagulation/fibrinolysis parameters even after several years without therapeutic intervention.

P2-d2-1191 Thyroid 8

Clinico-pathologic characteristics and treatment of differentiated thyroid cancers in children

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Background: Differentiated thyroid cancer(DTC) represent 0.5- 3% of all childhood malignancies. Papillary cancer(PC) comprises 90% to 95% of DTC, whereas medullary cancer (MC) is diagnosed in 5% to 8% and undifferentiated tumors are extremely rare.
Objective and hypotheses: We evaluated clinico-pathologic characteristics and treatment outcomes of 50 children with DTC treated at our unit between 1982 and 2013.
Methods: Fifty patients (30 girls, 20 boys) were evaluated retrospectively. Numbers of the patients diagnosed (after excluding patients with MC and history of radiotherapy) per each 10 years during study period were evaluated
Results: Mean age at diagnosis was 10.8±3.6 (range 1.3 to 18.2) years. Eight patients had a history of radiotherapy. PC was the most common(84%), followed by folicular cancer(8%) and MC(8%). There was an increase in numbers of cases especially during the last 3 decades as 6 patients(15.8%), 7(18.4%) and 25(65.8%) respectively. The mean tumor diameter was 2.4±1.8 (range 0.2-7) cm and nine tumors were microcarcinomas. At diagnosis, the incidence of capsule invasion, lymph node metastasis and lung metastasis were calculated as 60%, 40% and 12% respectively. Total, subtotal and unilateral thyroidectomy were performed in 36, 13 and 1 patients, respectively. During the follow-up, pulmonary metastasis were observed in 3 patients, cervical lymph node metastasis in 1 and mediastinal in 1 patient. Radioiodine therapy(RAI) was given to 37 patients with DTC in a total dose of 13-570 mCi. A total 12 patients took a second or more dose of RAI treatment for lymph node and distant metastasis. The mean follow-up period was 5.2±4.1 (range 0.4- 14.1) years. Two patients(one PC and one MC) died with pulmonary and mediastinal involvement.
Conclusions: Although thyroid cancer is a rare in childhood, we found increasing numbers of cases of DTC diagnosed in the last 10 years at our institution.

P2-d2-1192 Thyroid 8

Refetoff syndrome associated to common variable immunodeficiency and psoriasis: a case report

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Introduction: A 17-year-old adopted Brasilian boy with common variable immunodeficiency and psoriasis presented, during the follow-up, high levels of thyroid hormones with normal TSH values, positivity of anti-TPO antibodies and an ultrasound image characterized by the presence of two nodules.
Case study: The thyroid scintigraphy (99-MTC-pertechnetate) reported: "Gland in situ with slight asymmetry of the two lobes for the prevalence of the right one and normal distribution of the tracer" and we found normal levels of TSH after TRH-stimuli with very high levels of fT3 and fT4. The simultaneous absence of clinical signs of thyroid dysfunction raised the suspicion of a resistance to thyroid hormones. So the genetic study of thyroid hormones receptors was started through PCR and sequencing of the coding regions and intron-exons junctions of the THRB gene. The results was the presence, in the exon 9 of the THRB gene, of the mutation M313T due to a replacement cytosine-threonine (ACG-ATG) in etherozygosis. The introduction of a threonine is responsible for a slighter bound of the thyroid hormone T3 to his receptor. In addition an unusual polymorphism rs13063628 was found in etherozygosis in position IVS9+9bp. The molecular genetic response is compatible with the Refetoff syndrome, a very rare syndrome characterized by a mutation of the THRB gene responsible for a generalized resistance to the T3 nuclear receptor and sensorineural deafness.
Conclusion: Refetoff syndrome is usually associated to autoimmune diseases like vitiligo, thyroiditis and Graves' disease. The association with common variable immunodeficiency and psoriasis has never been described in literature before, and for this reason it is useful to research not only autoimmune diseases but also disorders of umoral and cellular immunity in the follow-up of these patients.

P2-d2-1193 Thyroid 8

What value of capillary TSH on screening should trigger referral for venipuncture in preschool and school-aged children with Down syndrome?

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Background: Annual capillary TSH (cTSH) screening in children with Down syndrome (DS) is now practised in all health boards across Scotland from the age of one year in order to pre-empt the development of hypothyroidism. We are aware that our cTSH cut-off level of ≥ 4 mU/l results in normal venous (v) fT4 and TSH in many children with borderline cTSH elevation and wish to minimise distress from unnecessary venepuncture.
Aims: To investigate if there is a threshold for cTSH below which low vfT4 (< 9 pmol/l) and/or frank vTSH elevation (>10 mu/l) are unlikely so that re-screening in 6 months might be more appropriate than immediate referral for venepuncture.
Methods: Review of proformas from all children with DS who were referred via our screening programme between January 2003 and March 2013. Comparison of cTSH with vfT4 and cTSH values in preschool (< 5 years) and school-age (≥5 years) subjects.
Results: 99 patients (50F:49M) were identified, 76 school-age and 23 preschool, with mean (range) age at referral 9.4 (0.9-18.1) years.

cTSH (mu/l)[n]	vfT4 (pmol/l)	vTSH (mu/l)	No.with vfT4<9pmol/l		No. with vTSH >10mu/l	
			<5yrs	>5yrs	<5 yrs	>5yrs
4-5.9 [51]	13.8 (7.5-20.0)	7.6 (1.1-25.9)	0	1*	4**	9***
6.0-10.9 [24]	12.8 (8.5-18.0)	16.1 (1.5-92.0)	0	3	3	12
10.9-20.0 [10]	12.3 (9.9-17.7)	17.5 (2.7-59.0)	0	0	0	9
>20.0 [14]	8.5 (4.4-14.6)	85.2 (14.7-151.0)	1	3	3	9

[Biochemical data on 99 patients by cTSH]

*One boy aged 15.8 yrs at referral with cTSH 4-5.9 mU/l had vfT4 7.4pmol/l and vTSH 11.2mU/l but no symptoms. He did not begin treatment and had normal vfT4 and vTSH 5 months later.
**vTSH values 10.7, 11.6, 12.5, 12.8 mU/l
*** median(range) vTSH 14.7 (10.4-25.9)mU/l
Conclusions: Almost all patients with a cTSH 4-6mU/l have normal vfT4 but vTSH is significantly elevated (>10 mU/l) in a minority. School-aged children referred with cTSH 4-6mU/l could be rescreened in 6 months, but immediate venous testing is indicated in preschool children with cTSH 4-6mU/l for the early detection of significant vTSH elevation in this vulnerable age group.

P2-d2-1194 Thyroid 8

Clinical features of children with congenital hypothyroidism due to thyroglobulin deficiency

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Background: Thyroglobulin (TG) deficiency is an autosomal-recessive disorder that results in thyroid dyshormonogenesis. Although congenital hypothyroidism (CH) is the most frequent endocrine disease in infants, with a prevalence of 1: 2.000-1: 4.000 in newborns; thyroglobulin deficiency is a rare disorder (1:40 000- 1:100 000) it is characterized by lower serum TG in relation to the degree of TSH stimulation, negative perchlorate discharge test and dilated endoplasmic reticulum (ER) with induction of ER molecular chaperones.
Objective and hypotheses: We aimed to present clinical features of 4 thyroglobulin deficiency cases.
Methods: In all patients, serum FT4, FT3, Tg, anti-TPO and anti-TG levels were studied. All patients were evaluated by thyroid ultrasonography.
Results: Clinical spectrum of the resulting phenotypes ranges from euthyroid to severe hypothyroidism.
Conclusions: Cases of congenital hypothyroidism due to thyroglobulin deficiency should be noted that may be euthyroid at birth.History of lumb in the neck in the neonatal period, should be evaluated in terms of the thyroglobulin deficiency. Family members of the cases should be investigated in terms of the thyroglobulin deficiency.

P3-d1-1195 Adrenals and HPA Axis 8

The clinical charateristics and genetic analysis of Allgrove syndrome in 3 Chinese cases

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Background: Allgrove syndrome is an autosomal recessive disease caused by mutations in the gene AAAS encoding ALADIN protein, characterized by the triad of adrenal insufficiecy, achalasia and alacrima.
Objective: To study the relationship between the phenotype and genotype of Allgrove syndrome through the sequencing results of 3 patients and the literature review.
Methods: We reported 3 patients' clinical features and mutations of ALADIN gene, reviewing the literatures.
Results: These 3 patients aged from 2 to 7 years old had the triad of adrenocortical insufficiency, alacrima and achalasia, diagnosed with Allgrove syndrome. Only case 1, who was 7 years old and coming from a consanguinity family, had neurological manifestations and she took high dose hydrocorticoid -acetate 70 mg/m^2.d to get control.
Case 1 underwent a surgical operation to lighten the symptoms of achalasia.

Case 2 took the conservative treatment without surgery, vomiting progressed gradually.
The AAAS genes of patients were sequenced. There were the same homozygous mution of c. 771 del. (p.Arg258GlyfsX33) in case 1 and 2; case 3 carried the homozygous mutation of c. 1366 c > T, p. Q456 *. Reviewed literatures revealed that the mutation of c.771del. only reported in Chinese population including a Hong Kong case who was a heterozygous mutation. Regardless of children and adult, including this cases report, we did not find a correlation between gene and clinical manifestations.
Conclusion: The 3 patients of Allgrove syndrome is diagnosed by the typical triad. Pediatric AAAS is more classical, with triad. Neural symptom is more common in late onset patients and adult patients. The c. 771del. mutation may be the hot spot in Chinese AAAS.

P3-d1-1196 Adrenals and HPA Axis 8

Pregnancy in women with CAH and women at risk of having children with CAH

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Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessively inherited metabolic disorder caused by the impairment of cortisol production and excess androgen production. Androgen excess leads to ambiguous genitalia in female fetuses and subsequently poor fertility outcome.
Objective and hypotheses: The aim of our study was to assess the fertility outcome in classic CAH patients with abnormal genotype and the women at risk of having children with CAH
Methods: The data presented is taken from the ongoing CAH study (BT/PR7205) cohort of hundred and two patients approved by Institute ethical committee. Genotyping was done by PCR and RFLP method to find out the underlying mutations of CYP21A2 gene.
Results: There were 7 pregnancies during the last three years in this CAH cohort. These 7 women with classic CAH were on medication Four had abnormal genotype with compound heterozygosity. One had normal genotype and two have to be confirmed. Six patients have delivered 5 vaginal deliveries and 1 CS (2 boys & 4 girls). One is expecting. Two families with CAH affected children (3 children with SW CAH) had also sought medical attention for the future pregnancy. In the first case, second pregnancy prenatal diagnosis revealed that one of the twins was a carrier. Molecular genetic analysis revealed that the patient harbored the compound heterozygous CYP21A2 gene mutations of p.P30L, intron 2, p.I172 N , p.A356W. Both the parents were found to be carriers. 2nd family came for evaluation during third month of pregnancy because they had lost two elder children during infancy (one girl & one boy) with diarrhoea and vomiting. The third baby girl was also found to ambiguous genitalia and SW CAH. Both parents were found to be carriers for the severe mutations of CYP21A2 gene.
Conclusions: All the six children born to mothers with classic CAH had normal external genitalia. Among the 3 children born to women who had earlier delivered CAH affected children, 1 had SWCAH.

P3-d1-1197 Adrenals and HPA Axis 8

Pubertal suppression with added growth hormone (GH) treatment to protect final height potential in 2 brothers with 11β-hydroxylase deficiency (11β-OHD)

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Background: 11β-OHD (mutations in CYP11B1) accounts for about 5% of virilising congenital adrenal hyperplasia. In boys the lack of urinary salt-wasting results in relatively late diagnosis compared with 21-OHD (CYP21). Patients typically have advanced bone age and likely compromised final height on presentation with premature virilisation, and may develop central precocious puberty (CPP). Suppression of CPP and adjunctive treatment with GH to protect final height potential has been reported in girls with 21-OHD. We report a similar approach to treat 2 brothers with 11β-OHD.
Objective and hypotheses/methods: Clinical case studies.
Results: The index patient presented age 4 yrs with Tanner stages G4, PH3, Testis volumes (TVs) 5ml, Ht 123 cm (+4.5 SDS), bone age 11.5 'yrs'. Blood and urine steroid hormone profiles revealed diagnosis of 11β-OHD,with raised serum testo. (2.6 nmol/L) and suppressed plasma renin activity (PRA). Father caucasian HtSDS +0.95; Mother Ghanain HtSDS +2.66; MPH +1.70 SDS. His 7 yr old brother (Ht 141.6 cm / +3.8 SDS; G1, PH2, TVs 2 ml) screened positive for 11β-OHD on urine and blood tests. Treatment with hydrocortisone (x3/day) reduced 11-deoxycortisol to target and suppressed Testo. and PRA in both patients.CPP evolved (increased TVs) in the index patient; Triptorelin (11.25 mg IM/3-mthly) and GH (1mg/d s.c.) started age 8.7 yrs, Ht 152 cm, +3.75 SDS. His brother started similar treatment age 10.1 yrs at 4ml TVs. Serum IGF-I was targeted close to upper level ref.range. Triptorelin was stopped in both boys after 3 years, and GH treatment 3 months later. Subsequent pubertal progress has been normal. Although both experienced significant gynaecomastia. The older brother has undergone cosmetic surgery. Current heights: 176 cm age 12.9 yrs , and 178 cm age 14.8 yrs - approaching normal final height outcomes. Molecular studies are in progress.
Conclusions: Pubertal suppression with GH supplementation may protect final height potential in 11β-OHD.

P3-d1-1198 Adrenals and HPA Axis 8

Cyclic hypercortisolism - a case presentation

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Introduction: Hypercortisolism is a rare condition in childhood.
The diagnosis is often difficult.
Case study: We present a 7 year old girl who was presented with recurrent episodes of rapid increasing weight without a change of the eating behavior. The episodes started six month ago and occurred every few weeks. The patients history was uneventful, especially the growth was parallel the 25th percentile which is also the mid parental height.
The clinical examination showed a healthy 7 year old girl with no extreme overweight (height 119 cm, weight 27 kg, bmi 19 kg/m² = 1,48 SDS), there was a buffalo neck and hirsutism but no striae and a normal blood pressure. In several appointments we could not reproduce the reported weight gains and found a quite stable bodyweight.
The laboratory workup showed recurrent normal to slightly elevated levels for cortisol (8 - 22 µg/dl norm 6,4-17,7) but low levels for ACTH. Cortisol salivary samples showed once nearly normal and the other time pronounced elevated levels at midnight. Urin cortisol (from 24h collection) was highly elevated.
The ultrasound and an MRI of the adrenals showed no structural abnormalities.
Because of the cyclic character of the symptoms, the acth independent hypercortisolism and the age of our patient we thought about primary pigmented nodular adrenocortical disease (PPNAD) and did the molecular analysis of the PRKAR1A- gene and found a heterozygous alteration.
Conclusion: PPNAD is part of the carney complex which is reported to show a cyclic pattern of acth independent hypercortisolism and the onset of the symptoms is at a mean age of 18 years. An inactivating heterozygous germ line mutation of PRKAR1A is observed in about two-thirds of carney complex patients.
In our case it was first and foremost the persistence of the parents to find the diagnosis at this early stage because the main features of hypercortisolim were less marked. Now we are discussing about the timing of the adrenalectomy.

P3-d1-1199 Adrenals and HPA Axis 8

Congenital adrenal hyperplasia: a review of 91 cases

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Background: Congenital adrenal hyperplasia (CAH) is a genetic endocrine disease how describes a group of inherited autosomal recessive disorders characterized by enzyme defects in the steroidogenic pathways that leads to biosynthesis of cortisol aldosterone and androgens. It is caused in more than 90% to a deficiency of the 21-hydroxylase activity.
Objective and hypotheses: The aim of this study was to analyze the epidemiological, clinical and genetic aspects of the CAH.
Methods: This is a retrospective study over a period of 11 years, from January 2003 to March 2013 including all patients with CAH followed at the unit of pediatric endocrinology of Children's Hospital in Casablanca. We excluded the cases lost sight.
Results: 91 cases of CAH were recruited. The mean age of our patients at diagnosis was 16.44 ± 40.34 Months. Parental consanguinity was found in 47 cases. 62 cases of CAH with a 46 XX karyotype was retained, 58 had a abnormality of sexual development, 18 cases were assigned boys at birth; 37 cases were presented with a salt wasting syndrome and 20 cases with a simple virilizing form. 29 cases had a 46 XY karyotype, including 2 cases assigned girl at birth; among these 29 cases, 26 had salt wasting syndrome. The non-classical form was found in 7 cases. The diagnosis of the 21-hydroxylase deficiency was found in 94.5% of cases, 3 cases had an 11-β hydroxylase deficiency, one case with a 3-β-HSD and one case of CYP11A1 deficiency. A genetic study was performed in 36 cases; we received 28 results the rest is in progress. The most frequent mutation in our series is the Q318X mutation, found in 29.50% of the affected alleles. Homozygous patients represent 64.8% of cases. The treatment was maintained in all patients, associated with surgical treatment in patients with disorder of sexual development.
Conclusions: The heterogeneity of clinical, pathological and genetic forms makes the management of CAH very challenging. Hence the importance of genetic counselling.

P3-d1-1200 Adrenals and HPA Axis 8

Normal urinary free cortisol as pitfall in diagnosis of Cushing disease in children: alternative workup options

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Background: Cushing disease, a rare cause of weight gain and growth deceleration in children, may be diagnosed by elavated urinary free cortisol (UFC).
Objective and hypotheses: To describe Cushing disease with normal UFC and suggest alternative workup options.
Methods:
Patient 1 - Nine years old boy with altered behavior, obesity and blunted growth. On physical examination truncal obesity and hyperpigmentation. UFC normal in 3 different laboratories. Overnight 1 mg dexamethasone suppression test abnormal. 2 days 2 mg dexamethasone suppression test abnormal followed by CRH test abnormal. Midnight cortisol level elevated. 24 hours cortisol profile showed no diurenal variation. Normal pituitary MRI twice and suspected microadenoma in a third MRI. During operation an microadenoma on the opposite side to the one found on the MRI was removed but the pathology report was negative. Cortisol level dropped. Steroid therapy was began. During half a year he lost 10 kg and grew 7 cm.
Patient 2 - Thirteen years old girl with obesity and blunted growth. She lost 11 kg on diet before admission. On physical examination mild obesity and hyperpigmentation. UFC elevated. MRI showed pituitary maroadrnoma which was removed. 2 years later UFC and 1 mg dexamethasone suppression test were normal. 2 days 2 mg dexamethasone suppression test abnormal followed by CRH test abnormal. Pituitary MRI showed suspected microadenoma. During operation an microadenoma from the cavernous sinus was removed. The pathology report was positive.
Results: Both patients had cushing disaese although UFC was normal.
Conclusions: Normal UFC do not exclude the diagnosis of Cushing disease nor do normal MRI or normal pathology report. If clinical findings support the diagnosis alternative diagnostic options (including overnight 1 mg dexamethasone suppression test, 2 days 2 mg dexamethasone suppression test followed by CRH test, midnight cortisol level and 24 hours cortisol profile) should be considered.

P3-d1-1201 Adrenals and HPA Axis 8

Behavioural outcome of children with congenital adrenal hyperplasia treated and followed at UKM Medical Centre

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Background: Disease and treatment related complications may interfere with behavioral development in patients with Congenital Adrenal Hyperplasia (CAH). This has not been investigated in CAH patients at our centre.
Objective and hypotheses: To determine the behavioral outcome of children with CAH and to identify features that may influence it.
Methods: Twenty nine females and 20 males with CAH (ages 6-18 years) were compared to normal siblings (25 females and 17 males). Behavioral outcome was measured by parent reports on the Child Behavior Checklist questionnaires(CBCL). Information about clinical and social features was obtained from medical reports and interview respectively.
Results: Mean age at diagnosis for males and females with CAH was 9.8 ± 2.29 months and 9.7 ± 1.91 months respectively. Eighty five percent of males and 83.8% of females had salt wasting CAH whereas 15% of males and 17.2% of females had simple virilising CAH. Mean age at study entry for males and females with CAH was 11.6 ± 4.26 and 11.9 ± 3.43 years respectively. For male and female controls, it was 12.76± 3.419 and 12.24 ± 3.8 years respectively. The mean Total Problems score (which was the sum of the scores of 113 problem items in CBCL) was higher in females with CAH compared to that of controls (36.10 ± 22.74 vs 17.72 ±13.60, p=0.001). Similar findings were seen in Social Problems (4.21 ± 3.075 vs 0.76 ± 1.128, p=0.001) and Attention Problems syndrome scales (6.31 ± 3.96 vs 1.2 ± 1.44, p= 0.000). In males with CAH, the mean scores of the Total Problems, Anxious/Depressed and Social Problems scale were higher (51.75 ± 31.55 vs 22.35 ± 18.71, p=0.001; 5.60 ± 3.56 vs 2.06 ± 2.07, p=0.001 and 5.00 ± 2.88 vs 2.35 ± 1.99, p= 0.002 respectively).
Conclusions: Certain aspects of behaviour were compromised in CAH patients. Multiple logistic regression showed significant associations between certain areas of behavioral problems with total family income, marital status of the parents and gender.

P3-d1-1202 Adrenals and HPA Axis 8

Allgrove syndrome

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Background: Allgrove syndrome is a rare autosomal recessive disorder characterized by the association of the triad adrenal insufficiency, alacrimia and achalasia
Objective and hypotheses: The aim of our study was to analyze the clinical characteristics of this rare syndrome.
Methods: The medical records of eight patients (6M/2F) were reviewed.
Results: Mean age at diagnosis was 8 years, in one patient the diagnosis was delayed at 27 years although the clinical symptoms begin many years before. Adrenal insufficiency associated to alacrimia was the presenting symptoms in all patients, achalasia was present in 75%, growth retardation and/or pubertal delay were reported in 75%, 62.5 % of patients have neurological dysfunction mainly pyramidal syndrome. Deficiency anemia was noted in 75%.
Conclusions: Allgrove syndrome is a rare hereditary disease which may have fatal consequences if undiagnosed, an earlier diagnosis and adequate treatment of the patient and the genetic council for the family improve the prognosis of this disease.

P3-d1-1203 Adrenals and HPA Axis 8

Distribution of the most frequent mutations and clinical characteristics among children with 21-hydroxylase deficiency in South-Eastern of Turkey

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Background: Congenital adrenal hyperplasia (CAH) is a autosomal recessive disorders mainly due to defects in the steroid 21-hydroxylase (CYP21A2) gene. Although there was a close relationship between genotype and phenotype, it is not homogeneous disease in our region and there was no any study of the mutational spectrum on children with congenital adrenal hyperplasia.
Objective and hypotheses: Consanguineous marriages are the most common our region in Turkey. We aimed to determine the mutational spectrum in the south-eastern of Turkish children population.
Methods: The CYP21A2 active gene was analyzed in 65 unrelated patients with the 21-hydroxylase deficiency using PCR and RFLP.
Results: 65 children diagnosed with congenital adrenal hyperplasia were enrolled. Patients' ages ranged from 0-16 years of age. 37 patients were 46XX, 28patients were 46XY karyotype. The most common mutations In2G, Q318X, R356W, I172, P30L, V281L, V237E, M239K, P453S 1108ntdel, F306 +1 nt were screened in all of patients.
Conclusions: The distribution of mutation frequencies in our study was slightly different from those previously reported in Turkey. However, the presence of more than one mutation was found to be quite common in this study.This result might be due to consanguineous marriages are quite a lot of in our region.

P3-d1-1204 Adrenals and HPA Axis 8

A three generation family with low cortisol, CBG deficiency, chronic fatigue and pain, lipomatosis and behavioral alterations

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Background: CBG is the main transport protein for glucocorticoids in blood. CBG gene is a member of the serine protease inhibitor family, located at chromosome 14q32. Inherited CBG deficiency (MIM 611489) is a rarely recessive disorder, and the phenotype associated includes low cortisol levels, presence of normal ACTH levels, hypotension and fatigue, although the exact pathophysiological mechanisms involved remain uncertain.
Objective and hypotheses: We identified a family with a complex phenotype, that includes low free cortisol levels, lipomatosis, chronic fatigue, pain and CBG deficiency, with a segregation suggestive of a monogenic inheritance. Aim of the study is to explore which gene is involved in this complex disease suggestive to be hereditary.
Methods: We quantified the plasmatic concentration of CBG protein both in our family (n=9) than in a group of healthy controls (n=15) by using a commercial kit. Molecular analysis of four coding exons of CBG gene was performed by direct sequencing. Segregation analysis of parental alleles was performed through linkage analysis.
Results: Salivary and LC-MS/MS analysis identified very low free cortisol levels in two children and in the father, despite normal ACTH levels, with cortisol levels at the end of normal range in the sister and paternal grandfather. The maternal grandfather, the father and the two male children presented low plasmatic CBG levels. Paternal grandfather presented CBG levels at the end of the normal range. No mutations were identified in the CBG gene coding-regions. We identified only five SNPs. Linkage analysis identified a likely paternal transmission of the CBG alleles.
Conclusion: With the hypothesis that our family is affected by inherited CBG deficiency, molecular analysis of non-coding regions and functional studies of CBG gene will be performed. In addition, the involvement of supplementary gene-disease will be demonstrated by cGH array and exome sequencing analysis.

P3-d1-1205 Adrenals and HPA Axis 8

Reversible cause of cardiomyopathy in the paediatric age group: family history of ambiguous genitalia is the key of diagnosis

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Background: The World Health Organization classifies cardiomyopathy into four categories:
1) dilated cardiomyopathy;
2) hypertrophic cardiomyopathy;
3) restrictive cardiomyopathy, and
4) arrhythmogenic right ventricular cardiomyopathy.
Objective: To report unusual reversible cause of cardiomyopathy. Clinical Presentation and Intervention: A 21 months old boy admitted to our hospital through Emergency Department with history of penile enlargement and progressive darkness of skin for the last 10 months. Clinical examination showing good body belt with weight of 13kg in75th percentile height 92cm which is above 97th Percentile, high BP 139/90 above 95th percentile, hyperpegmentaion of gum with darkness of skin, facial acne, penile enlargement with 8,7cm length above 90th percentile with scrotal hyper pigmentation (testicular size pre pubertal with no pubic hair) Laboratory investigation showing high ACTH 507pg/ml(normal range 5-60pg/ml)with low serum cortisole 42.4nmol/L (55-248nmol/L), 17hydroxyprogesrerone 67nmol/l (0.3-2.5nmol/L), Androstendione more than 70nmol/L (2.4-12.6nmol/L)Testosterone 5.49nmol/L high for his age (0.1-1.12nmol/L) FSH 0.5mIU/ml, LH 0.3mIU/ml, Deoxycorticosterone was269ng/dl(4-49ng/dl), Advanced bone age 5-6 years, Echocardiography showing mild dilated cardoimyopathy. Patient diagnosed as case of congenital adrenal hyperplasia, 11betahydroxlase deficiency, hydrocortisone treatment started with anti hypertensive medication. In 9 month follow-up wean of antihypertensive medication, repeated Echocardiography was normal, Acne disappear, Skin darkness and hyperpegmentation improved and patient currently receiving hydrocortisone tablet 5mg Am,2.5mg noon and 2.5mg Pm.
Conclusion: CAH type 11betahydroxylase deficiency can be missed especially in male until present with complications such as that related to hypertension, hypocortisolism and/or androgen excess that leads to precocious puberty, all these can be avoided by checking BP in well baby clinic visit.

P3-d2-1206 Adrenals and HPA Axis 9

Unusual biochemical presentation of 17-alpha hydroxylase/17,20-lyase deficiency in a recent immigrant from Ecuador: a case report

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Introduction: 17 alpha hydroxylase/17,20-lyase deficiency is an autosomal recessive disorder caused by P450c17 defects in the CYP17A1 gene.
Case study: Patient is an 18 yrs old Hispanic female, who presented with primary amenorrhea and absent breast and pubic/axillary hair development, no hepatosplenomegaly, normal blood pressure. Physical exam was otherwise unremarkable. Family history was non-contributory. Aldosterone and electrolytes levels were normal and there was no previous history or current presentation of hypertension. Initial laboratory values with normal karyotype 46 XX, elevated FSH and LH and very low estrogens and AMH suggestive of primary ovarian failure. Adrenal and Ovarian AB were negative. Chest X ray was normal; she was treated with INH for positive PPD. Basal level of 11-deoxycortisol was elevated at 126 ng/dl (< 107 ng/dl) with stimulated levels at 146 ng/dl. Basal level of deoxycorticosterone was elevated at 127 ng/dl (< 23 ng/dl) with stimulated level of 177 ng/dl. The remaining basal adrenal hormones were remarkable for elevated ACTH 256 pg/ml and low pre and post cortisol at 0.7 mcg/dl and 0.8 mcg/dl respectively. DHEA, DHEAS, 17- hydroxyprogesterone and 17 hydroxypregnenalone, androstendione, testosterone, DHT, E2, E3 remained almost undetectable low prior to and after ACTH stimulation. The normal level of BP, normal electrolytes and aldosterone, elevated baseline 11 deoxycortisol may be representative of partial 17alpha hydroxylase deficiency and complete 17,20 lyase deficiency. Genetic analysis in progress.
Conclusions: Combined 17 alpha hydroxylase/17,20-lyase deficiency can present with various phenotypes and should be suspected in cases with normal blood pressure and combined ovarian and adrenal failure.

P3-d2-1207 Adrenals and HPA Axis 9

Adrenocortical carcinoma in a child

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Background: Adrenocortical carcinomas are rare comprising 0.2% of childhood cancers. We report on a child with adrenocortical carcinoma with Cushingoid features and virilization
Objective and hypotheses: To describe the clinical features and investigations in the case.
Methods: A four year and ten month female child presented with convulsions, hypertention and a right sided hypochondral mass. The patient had features of Cushings syndrome and prominent virilisation
Results: The urinary cortisol concentration was greater than 2069 nmol/l, with a serum ACTH which was suppressed (< 5 ng/l). The serum testosterone and DHEA were elevated (testosterone >55 nmol/L and DHEA >27 umol/L). Both serum aldosterone and renin were elevated (1182 pmol/l and 263 mIU/l respectively). The bone age was advanced at 10 years. CT of the abdomen confirmed the presence of a mass (with calcifications) arising from the right adrenal gland. At surgery, a large mass adherent to the right kidney was found. The entire tumour (measuring 170 x 125 x 85) and right kidney were removed. Apart from the renal involvement, there was no evidence further dissemination of the tumour. Histology confirmed the presence of a low grade adrenal carcinoma.
However, there was evidence of lymphovascular invasion and breeching of the adrenal capsule by the tumour. The hormonal studies normalized postoperatively.
Although the tumour was completely excised, given the generally grave prognosis of adrenocortical tumours and high risk for recurrence, chemotherapy was initiated (mitotane, cisplatinum, doxyrubicin and etoposide).
Conclusions: The presence of virilisation in childhood Cushing's syndrome should lead one to entertain the diagnosis of adrenocortical carcinoma.

P3-d2-1208 Adrenals and HPA Axis 9

A novel microdeletion in *NR0B1 (DAX1)* gene in a boy with congenital adrenal hypoplasia

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Introduction: Adrenal Hypoplasia Congenita (AHC, OMIM#300200) is a rare disorder that can be inherited in an X-linked or autosomal recessive pattern. In X-linked AHC, adrenocortical failure is caused by deletions or point mutations in the *NR0B1 (DAX1*) (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1) gene (OMIM*300473) located on the X chromosome. Deletion of *NR0B1 (DAX1)* may be part of a larger contiguous deletion including dystrophin and glycerol kinase (*GK*) genes.
Objective and methods: We present a boy with AHC who came to our attention at the age of 25 days in a severe state due to prolonged vomiting and progressive dehydration. Laboratory studies showed prominent hyponatremia and hyperkaliemia but not hypoglycemia. Primary adrenal insufficiency was confirmed, with low serum cortisol levels and high plasma ACTH levels. Hydrocortisone therapy with saline and glucose infusions was started immediately after blood collection. Standard PCR method was used to amplify two exons of the *NR0B1 (DAX1)* gene. Array CGH was used to confirm the PCR results.
Results: Molecular analysis of the *NR0B1 (DAX1)* gene revealed a novel deletion of the *NR0B1 (DAX1)* together with the *MAGE* genes. This genetic defect was not present in the patient's mother.
Conclusions: We show that *NR0B1 (DAX1)* gene analysis is important for the confirmation of the clinical diagnosis of AHC and highlight the role of genetic counseling for families of AHC patients, particularly those with X-chromosome microdeletions, covering more than *NR0B1 (DAX1)* alone.

P3-d2-1209 Adrenals and HPA Axis 9

A case of adrenal insufficiency due to isolated ACTH deficiency met the diagnostic criteria of orthostatic dysregulation

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Introduction: Various isolated pituitary gland deficiencies have been reported, but isolated ACTH deficiency is a serious life-threatening disease. Isolated ACTH deficiency causes secondary adrenal insufficiency, and steroid supplementation is an essential treatment for an affected child. In addition, the isolated ACTH deficiency-affected child has various symptoms, and may consult a medical institution with the chief complaint of so-called malaise.
Case study: Here, we report a case of a girl who complained chiefly of headache, poor appetite and lethargy in her puberty. From her symptoms and rising test, Orthostatic Dysregulation (hereafter, OD) was diagnosed and treatment was started, but there was no response to drug treatment, and from subsequent tests, it was clear she had adrenocortical insufficiency due to isolated ACTH deficiency. Because the early-morning blood level of ACTH in the affected child was a low value of 4 pg/ml, and after further detailed examination, urinary cortisol concentration in urine was lower than 4.5 µg/day, and in a CRH load test, there was a low response, i.e., the ACTH basic level was 2.2 pg/ml and the top level was 3.7 pg/ml, we diagnosed isolated ACTH deficiency and secondary adrenal insufficiency. After starting adrenocorticosteroids there was an effect, and her symptoms almost resolved on the next day.
Conclusion: OD and psychosomatic malaise of puberty is a frequent diagnosis, but it is also necessary to consider adrenal insufficiency as a differential diagnosis, and exhaustive tests are required for an affected child who does not respond to medical treatment.

P3-d2-1210 Adrenals and HPA Axis 9

Presentation of two brothers with diagnostic problems: P450 oxidoreductase deficiency?

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Background: P450 oxidoreductase deficiency (PORD), is a rare and complex form of congenital adrenal hyperplasia (CAH) that results from partial and combined impairment of steroidogenic enzymes.
Case report 1: A 2-month-old male infant referred as hypospadias. He was born at term from consanguineous parents with intrauterin growth retardation. The mother had no problem during pregnancy. The external genitalia had penoscrotal hypospadias with chordee and both testes were normally sized within the scrotum. No other dysmorphic signs, skeletal malformations were observed. The karyotype analysis was 46, XY. Biochemical and baseline hormonal findings were normal except for slightly high 17-OHP (9,3 ng/ml). ACTH stimulation test revealed similar to non-classical CAH with no clinically compatible. In follow-up, when he was 33-months-old we performed synacthen test again. Basal ACTH was at the upper limit of the normal range, with elevated 17-OHP and progesterone levels, while androgen levels were low; basal cortisol was normal but stimulated was low. PORD was considered and treated with hydrocortisone. However any mutation of POR was not detected.
Case report 2: The sibling of case1, because of this the patient brought to our clinic postnatally. His physical examination was completely normal. Biochemical and baseline hormonal findings were normal except for slightly high 17-OHP like his brother. Also adrenal insufficiency demonstrated with repeated ACTH tests and started therapy.
Conclusion: These patients who were presented with varied physical and biochemical phenotype of impaired steroidogenesis, showed us that the diagnosis of disorders of adrenal steroidogenesis is not always easy. Although the

etiology of the clinical signs remained undefined because of the variability in phenotype and steroid hormone profile in PORD and the risk of adrenal insufficiency, clinicians should be alert to this potential diagnosis.

P3-d2-1211 Adrenals and HPA Axis 9

Overweight in Addison disease: a case report

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Background: Addison's disease is a rare endocrine disorder in children characterised by weakness, increased pigmentation of the skin, low blood pressure, nausea, vomiting and usually a weigth loss.
Objective: We present a case of an overweigth prepubertal child of eleven years old, until that moment with history of good health,arrived at our hospital by the suddenly onset of gastrointestinal symptoms complicated in few hours with dehydratation, anuria and severe metabolic acidosis.
Subject: At first examination he presented the following auxological parameters: weigth 53 Kg (+ 2,23 SD),eight 142,5 cm (- 0,66 SD), BMI 26,28 (+ 1,68 SD) and additional symptoms included brozed complexion, dehydrated skin, mydriasis, areflexia.
Results: Blood test showed low levels of serum sodium and clorum, high levels of serum potassium. Suspecting primary adrenal insufficiency we dosed ACTH, cortisol, aldosterone and renin levels. WE found very high level of ACTH, low level of cortisol after stimulation with ACTH, high serum renin with low serum aldosterone and CT scan demonstrating bilateral adrenal hypotrophy. After those results the patient began therapy with hydrocortisone and flurocortisone acetate with rapid improvement of symptoms.
Conclusions: We describe this case because the Addison's disease onset is not associated with a weight loss. Therefore, in case of suspicion of primary adrenal insufficiency, it must pay attention to symptoms like electrolytic and metabolic abnormalities withouth excluding the diagnosis in presence of overewight.

P3-d2-1212 Adrenals and HPA Axis 9

Adrenal hemorrhage after abdominal blunt trauma in a 5-year-old boy

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Objective and hypotheses: Adrenal gland hematoma is rare lesion in children. But children have relatively large adrenals that may risk for haemorrhage at abdominal trauma.
Methods and results: We report a 5 years old child with adrenal haemorrhagy and transient transaminaz elevation after abdminal blunt trauma. The patient complained of severe right-sided flank pain, no nausea, vomiting and on physical examination no direct tenderness. Hematocrit, aspartat and alanin transaminase levels were 33.6%, 402 and 224 U/l. He had no red blood cell in the urine test. Abdominal ultrasound (US) was showed iso-hypoechogenic mass within the right adrenal space and contrast-enhanced computed tomography had no change on the same adrenal lesion and not any signs of intraabdominal solid organ injuries. The cortisol level was normal (11.2 ug/dl) early morning. Transaminase levels started to decrease after 3 days.
According to the one-month US follow-up, the hematoma was almost completely absorbed.
Conclusions: The incidence of adrenal hematoma is range from 0,22 to 4% of children detected for blunt abdominal trauma, but in autopsy series of blunt abdominal trauma cases increases to 7 to 25 %. Abdominal trauma, surgical complication, anticoaguland therapy, child abuse, bleeding into a tumour, sepsis and shock may be detected. Adrenal hemorrhage is frequently unilateral and the incidance of is much higer on the right side with liver injury. Unilateral injuries have limited clinical significance and bilateral adrenal hemorrhage may occur with acute adrenal insufficiency. CT is the best diagnostic technique and US is very useful in follow-up examination. Contrast-enhanced CT is useful to diagnosis of adrenal hematoma from adrenal neoplasms. Isolated adrenal gland injury is rare in the pediatric population after blunt abdominal trauma. But the lower chest injuries and solid viscous injury should alert to the possbilty of adrenal gland affected.

P3-d2-1213 Adrenals and HPA Axis 9

Effects of dexamethasone treatment in an 18-year-old boy with congenital adrenal hyperplasia due to 11β-hydroxysteroid dehydrogenase type 1 deficiency: case report

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Background: Congenital adrenal hyperplasia due to 11β-hydroxysteroid dehydrogenase type 1 deficiency (CAH-HSD11β-1) is a rare disorder,in which lack of the enzyme causes inactivity converting cortisone to cortisol.The result of this deficiency is an increased level of ACTH.Clinically male patients present the GnRH-independent precocious puberty with rapid growth and advanced bone age.
Objective and hypotheses: We present the case of 18-year-old man,who was treated of CAH.
Methods: When the boy was 6 ys,he was diagnosed because of precocious puberty.The height (136 cm/ +2,6 SD),weight(BMI - 16,8 kg/m2), bone age - 11,5 ys,advanced puberty by Tanner stages:Pub 2, Ax 1, volumes of testis 2ml were measured during the physical examination. In laboratory tests the patient had decreased ratio metabolite of cortisol to cortisone in urine, elevated adrenal androgens (SDHEA-16,85µmol/l,testosterone-1,4 nmol/l),17-OHP-6,04nmol/l and normal level of cortisol(197 nmol/l) and ACTH(40 pg/ml).
Results: The hydrocortisone had been administered orally in dosages of 12mg/m^2/day in three divided doses for 2 months without decreased level of androgens. After that, the using therapy with dexamethasone(0,5 mg in two divided doses orally)caused decreased level of androgens, slowed growth during first year of treatment and height near the normal "high" curve(90 centile) in following years. The other result of that therapy was slow down progression of bone age. Actually that young man is 18 ys and his height is 182,4 cm(75-90c), normal puberty.A bone age is approximately equal to chronologic age.
Conclusions:
1) The preferred glucocorticoid for chronic treatment of the congenital adrenal hyperplasia due to 11β- hydroxysteroid dehydrogenase type 1 deficiency is dexamethasone, which it is not metabolized by oxidation in different tissues in contrast to hydrocortisone.
2) For the purpose of prevented hyperandrogenism in children and adolescents it is important to treat the patient by antiandrogenic drugs.

P3-d2-1214 Adrenals and HPA Axis 9

Corticosteroid insufficiency provoking ventricular arrhythmia

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Background: Recurrent syncope may be a presenting feature of a cardiac illness, recurrent hypoglycaemia or both. We report a 13 year old boy presented with recurrent fainting episodes with corticosteroid insufficiency (CI) and prolonged QT (PQT) interval followed by ventricular arrhythmia (VA).
Case report: A 13 year old boy of non consanguineous parents had recurrent syncope which improved in response to oral or intravenous dextrose despite no documented hypoglycaemia. He has nocturnal enuresis started at the age of 10 years suggesting syncopal episodes during sleep. He was admitted in PICU with one of these episodes and attached to cardiac monitor. His investigations revealed strikingly low 9 am cortisol and a flat response to ACTH stimulation test (Cortisol: 0.5 nmol/l) and ACTH of 0.05 pmol/l. He had,

otherwise, normal baseline anterior pituitary functions. Hydrocortisone replacement therapy has been started but he rapidly developed VA, classic ECG features of PQT3 syndrome and progressed to cardiac arrest. He was resuscitated and his arrhythmias were only successfully controlled by inserting intra cardiac defibrillator. Genetic tests of PQT syndromes have been arranged.
Discussion: PQT syndromes are caused by mutations of certain sodium or potassium channel genes. It was suggested that hormonal modulation of these ion channels of cardiac cells may mediate this ECG changes and provoke polymorphic ventricular tachycardia. In adults, a unique case (72 years) was reported to develop PQT interval and fatal VA with isolated ACTH deficiency. Though a transient CI is a recognized feature in some patients with acute severe illness, our patient had failed the repeat ACTH stimulation test 3 months later. Simultaneously a very low value of ACTH favoured the diagnosis of isolated ACTH deficiency in the absence of other pituitary hormonal deficiencies.
Conclusions: CI may provoke QT prolongation responsible for severe VA and may lead to sudden cardiac death.

P3-d2-1215 Adrenals and HPA Axis 9

Cushing syndrome due to multinodular adrenal hyperplasia: case report

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Cushing syndrome (CS) describes any form of glucocorticoid excess. Causes of CS include adrenal adenoma, adrenal carcinoma and multinodular adrenal hyperplasia (MAH). The physical features of CS are familiar. Central obesity, moon facies, hirsutism and facial flushing are seen in over 80% of adults. Striae, hypertension, musculer weakness, back pain, buffalo hump fat distribution, psychological disturbances, acne and easy bruising are also very commonly described (35-80%). ACTH independent multinodular adrenal hyperplasia is a rare entity characterized by the secretion of both cortisol and adrenal androgens. It is seen in infants, children and young adults, with females affected more frequently. Laboratuary findings include elevated plasma cortisol levels and normally or suppressed ACTH.
We present here 11.5 year old girl suffering from obesity and diagnosed CS due to MAH.
She was excessive weight gain in the last two years. Physical examination revealed short stature (height: 137 cm< 3p, SDS: -2.2), obesity (weight 55 kg (90-97 p), BMI 29.8 kg/m² >95p), hypertension (sys/dias 130/90 mm/hg, moon face, striae, buffalo hump and hirsutism. Laboratuary findings: glucose 87 mg/dl, total chollesterol 221 mg/dl, triglycerid 116 mg/dl, insulin 27.3 µU/ml, HOMA-IR 5.8 (↑), fT3 3.6 pg/ml, fT4 1.2 ng/dl, TSH 2.4 mIU/ml, ACTH 49.17 pg/ml, LH 0.1 mIU/ml, FSH 0.8 mIU/ml, estradiol 5.0 pg/ml, basal serum cortisol 35.4 µg/dl, after dexhametasone suppression test serum cortisol 22.4 µg/dl, 24 hour urine cortisol 797 µg. Radiological eveluation showed left adrenal multinodular hyperplasia and planned to adrenalectomy.

P3-d1-1216 Autoimmune Endocrine Diseases 4

Prevalence of hypothyroidism and celiac disease among children with diabetes mellitus

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Objective: Establish the prevalence of hypothyroidism and CD among children with DM as a result of selective screening.
Methods: During the three-year examination period (2010 - 2012) 556 children (270 girls/286 boys) aged from 1.0 to 17.5 yearswere examined. Indications for examination: new-onset DM and DM in combination with physical development delay, underweight, diabetic hand syndrome, clinical signs of malabsorption syndrome. TSH and TPO-Ab were measured as a screening for ATD, by the way a thyroid ultrasound was performed and serological markers were tested for the screening of CD (AGA IgA; AGA IgG, tTG IgA). While the diagnostic raising of specific antibodies biopsy was carried out. Histological examination was carried out by two independent morphologists using March classification.
Results: Increased level of TPO-Ab was detected in 148 (26.7%) of 556 children, of which 38 (6.8%) were known to suffered from autoimmune thyroiditis (AIT), 34 (6.1%) with AIT first found and in 76 (13.8%) showed an isolated increase of TPO-Ab without structural changes on thyroid ultrasound and euthyroidism. Out of 72 children with AIT (12.9%), 21 (3.8%) were in the state of euthyroidism, 29 (5.2%) - subclinical hypothyroidism, 22 (3.9%) - overt hypothyroidism. An increase of at least one of serological markers of CD above the reference interval was found in 166 patients (29.8%) and 11 (1.9%) children confirmed histological diagnosis of CD and 6 of them had asymptomatic disease course.
Conclusions: The prevalence of overt hypothyroidism (3.9%) in the outcome of AIT and CD (1.9%) in children with DM was above the population level, which confirms the effective of selective screening in this group of children; high incidence of TPO-Ab (13.8%) and mucosa of the small intestine (27.9%) in children with DM need to clarify their prognostic value having regard to long-term follow-up, as well as revising of dividing cut-of-point.

P3-d1-1217 Autoimmune Endocrine Diseases 4

Coincidence of Graves disease and Sjögren syndrome in a 16-year-old girl

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Introduction: In our outpatient clinic for pediatric endocrinology we saw a 16,2 year old girl with regularly occurring pain in the knee joint and muscle pain, concentration problems, weight loss, increased sweating and appetite as well as irregular cycle and dysmenorrhea for 6 months and most recently, daily pain in elbow and fingers increasing after physical activity. Occasionally dry eyes. Two-time marsupialization in the oral cavity after formation of ranulas.
Case study: The clinical examination revealed a goiter in otherwise unremarkable physical findings. Laboratory an ultrasound results showed Graves'disease with a hyperthyroid metabolic situation and in coincidence Sjögren's syndrome with abnormal antibody patterns and pathological Schirmer's test.We started treatment with methimazole, hydroxychloroquine and eyedrops against dryness.
Conclusion: Graves' disease and Sjögren's syndrome are chronic inflammatory autoimmune diseases with rare incidence children and adolescents. Both disorders can be associated with or merge into other connective tissue diseases such as Systemic lupus erythematosus, Rheumatoid arthritis, Myasthenia gravis and Scleroderma. Also there may be a correlation to autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), a subtype of autoimmune polyendocrine syndrome, in which multiple endocrine glands dysfunction as a result of autoimmunity. It is a recessive inherited genetic disorder attributed to a defect in the AIRE gene.

P3-d1-1218 Autoimmune Endocrine Diseases 4

Polyglandular autoimmune syndrome type II with adrenalitis, thyroiditis and ovarian failure in an adolescent girl

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Background: Polyglandular autoimmune syndrome type II (PAS-II) is characterized by the obligatory occurence of autoimmune Addison's disease in combination with thyroid autoimmune disease and/or type I diabetes mellitus. Primary hypogonadism, myasthenia gravis and celiac disease are also commonly observed in this syndrome. PAS-II occurs primarily in adulthood with peak prevalence in middle-aged women.
Patient: A 16 year old girl presented with fatigue, emesis, diarrhea, and hyperpigmentation. Diagnostic workup showed primary hypocortisolism, primary hypothyroidism, and primary hypogonadism with secondary amenorrhoe for 9 months. Unremarkable family history.

Results: Adrenal autoantibodies could be detected against steroid-c21-hydroxylase, indicating Addison's disease. Thyroid ultrasound and positive TPO-antiodies proved Hashimoto's thyreoidits. Treatment was initiated with hydrocortisone (15 mg/m^2), L-thyroxin 1 ug/kg/d. Within four months, the dose of hydrocortisone could be reduced to 6 mg/m^2. Hyperpigmentation disappeared within four months. Because of persisting amenorrhea, GnRH stimulation testing was performed which showed elevated LH and FSH indicating primary ovarian failure. Ovarian antibodies (p450c17hydroxylase and p450scc hydroxylase) were significantly detectable. Treatment was initiated with dienogest and ethinyl estradiol. Menses are now regularly.
Conclusions: In patients with Morbus Addison and secondary amenorrhea, autoimmune ovariitis should be considered as a part of the polyglandular autoimmune syndrome type II.

P3-d1-1219 Autoimmune Endocrine Diseases 4

Basal insulin requirement in children, adolescents and young adults using continuous subcutaneous insulin infusion (CSII)

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Background: Several reports have indicated the efficacy and safety of continuous subcutaneous insulin infusion (CSII), and during the past decade, CSII is widely used for patients with type 1 diabetes (T1D) in Japan. Patients with T1D are recommended to set proper amount of basal insulin dose. According to some reports, total basal insulin dose (TBD) is 30~50% of the total daily insulin dose (TDD) in adult.
Objective and hypothesis: The purpose of this study is to assess basal insulin requirement in children, adolescents and young adults with T1D.
Methods: The subjects were 39 Japanese patients with T1D(10 males and 29 females) who have been treated with CSII more than one year. Three subjeccts ware excludeed due to eating disorder, using other antidiabetic agents and pregnancy. Patients were devided into four age groups: < 6 yr (n=6), 6-11 yr (n=7), 12-17 yr (n=5), ≧18 yr (n=18). Basal insulin requirement were evaluated by their medical charts for each patients at Feb 2013.
Results: Average TBD were as follows: 6.4±2.9 U/day (< 6 yr), 13.1±6.7 U/day (6-11 yr), 35.3±10.7 U/day (12-17 yr) and 22.3±9.2 U/day (≧18 yr). adolescents with the age of 12-17 yr required significantly much amount of TBD compared with the other three groups. Average TBD/TDD was also significantly higher in the adolescent group (< 6 yr: 0.42±0.10, 6-11 yr: 0.48±0.10, 12-17 yr: 0.59±0.05 and ≧18 yr: 0.49±0.12).
Conclusions: Basal insulin requirement in type 1 diabetes accounted for 40~50% of TDD in this study except for adolescent group. In this period, it is necessary to increase the TBD deu to incease of insulin resistance caused by mainly growth hormone secretion. Adolescents with T1D required approximately 60% of TDD for their TBD even in CSII.

P3-d1-1220 Autoimmune Endocrine Diseases 4

A unique case of a patient with acute onset type 1 diabetes mellitus and two other autoimmune illnesses

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Introduction: While Type 1 Diabetes Mellitus (T1DM) is known to predispose an individual to other autoimmune diseases, this is the only known case report of a pediatric patient diagnosed with new onset T1DM during the acute emergence of two other autoimmune diseases.
Case study: A 15 yo previously healthy male presented with a two week history of bloody diarrhea and left lower extremity swelling and erythema. After initial evaluation and imaging, he was found to have multiple extremity venous thrombi requiring intravenous anti-coagulation therapy. During hospitalization, the patient was found to be homozygous for MTHFR deficiency and was also diagnosed with antiphospholipid antibody syndrome (APS) with anti-cardiolipin antibodies measured twice, more than six weeks apart. While ds-DNA antibodies were detected, repeat ANA and Crithidia luciliae immunofluorescence (CLIF) testing were negative. Patient had multiple guaiac positive stools and positive IBD-7 testing, leading to an EGD/colonoscopy that confirmed ulcerative colitis (UC). While undergoing bowel rest, the patient was started on peripheral nutrition and then noted to have persistent hyperglycemia (BG>300mg/dl). His HgA1C was found to be elevated (6.6%), and the patient had positive GAD antibodies. He was therefore diagnosed with T1DM and started on sq insulin therapy. The patient was discharged home on sq insulin, oral prednisone, pain medications, and at least 6 months of low molecular weight heparin injections.
Conclusion: This 15 yo male presented with an unusual case of Type 1 Diabetes Mellitus associated with two other autoimmune diseases (ulcerative colitis and antiphospholipid antibody syndrome). More research is needed concerning the genetic links between various autoimmune pathologies and the potential risks for clustered autoimmune illnesses. Providers should also be alert to the possibility of multiple autoimmune processes in children with new onset T1DM.

P3-d1-1221 Autoimmune Endocrine Diseases 4

Prevalence of autoimmune thyroid disease in children and adolescents with type 1 diabetes mellitus from Western Algeria

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Background: Type 1 diabetes mellitus (T1DM) is an auto-immune disease It is associated with other auto-immune endocrine disorders. Auto-immune thyroid disease is one of the most frequent auto-immune diseases associated with it.
Objective and hypotheses: To define the prevalence of thyroid autoimmune disease in West Algerian patients with type 1 diabetes mellitus .
Method: Blood samples were collected from 100 T1DM patients and 94 patients with T1DM - Coeliac disease, who are followed by the Oran Pediatric Department, Algeria. All patients are more than 15 years at the time of screening were included and whose diagnosis of T1DM was established before the 15 years age. All patients presenting thyroid disease were excluded. Sera of 100 healthy subjects served as controls. in each group, the number of the girls was equivalent to the number of the boys. Antithyroperoxidase antibodies (TPO-Ab), was determined by enzyme-linked immunosorbent assay. TSH and FT4 concentrations, thyroid echography were carried in subjects positives for TPO-Ab.
Results: Among of 100 patients with T1DM, 15 (9 girls, 6 boys) had positive TPO-Ab. one patient had evidence of subclinical hypothyroidism. Thyroid echography had revealed 4 goiters.
Among 94 patients T1DM-Coeliac disease, 11 (7 girls, 4 boys) had positive TPO-Ab. Three patients had evidence of subclinical hypothyroidism. Thyroid echography had revealed 4 goiters.
Among 100 controls, 7 (7 girls) had positive TPO-Ab. one patients had evidence of subclinical hypothyroidism. thyroid echography had revealed 1 goiters.
Conclusions: The prevalence of autoimmune thyroid disease in type 1 diabetic patients (15 %) is higher than in the general population (7 %). The screening of uto-immune thyroid disease should could be systemic in T1DM patients as the coeliac disease.

P3-d1-1222 Autoimmune Endocrine Diseases 4

Hyponatraemia in a teenager: a rare diagnosis

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Introduction: Hyponatremia is defined as a serum sodium level of less than 135 mEq/L and diarrhea is the most common cause of hypovolemic hyponatremia in children. The authors present a case of a teenager with symptomatic

hyponatremia with a less common cause.
Case study: A 17 years old teenager was admitted in the emergency department with abdominal pain, nausea and vomiting, associated with cough, asthenia, anorexia and weight loss (5 kg) in the last month. He had poor general appearence, obtundation, dry mucous membranes, poor peripheral perfusion, hypotension (BP< P5) and skin and mucosa hyperpigmentation. The laboratory findings showed renal dysfunction (Urea 100mg/dL, Creatinine 2.5mg/dL), severe hyponatremia (112mEq/L), hyperkalemia (5.9mEq/L) and metabolic acidosis (pH 7.22; pCO2 31mmHg; HCO3 12.7mmol/L) with normal glucose. He had a moderate pericardial effusion and bilateral pneumonia with pleural effusion. The patient started inotropic support with dopamine and norepinephrine and antibiotics. Plasma cortisol (4.4mcg/dl) and ACTH levels (948ng/dL) confirmed the diagnosis of primary adrenal insufficiency. He began replacement therapy with hydrocortisone and fludrocortisone, with gradual symptoms resolution. Abdominal CT showed adrenal hypoplasia, excluding hemorrhage and calcifications. Mycobacterium tuberculosis and HIV infection were excluded. No infectious agent was isolated. Anti-adrenal and anti-thyroid antibodies were positive, allowing the diagnosis of autoimmune polyglandular syndrome type 2 (adrenalitis with autoimmune thyroiditis, without diabetes mellitus).
Conclusion: Adrenal insufficiency is a rare disease, especially in children, and its clinical manifestations are due to glucocorticoid and mineralocorticoid deficiency. In most of the cases symptoms are nonspecific, requiring a high index of clinical suspicion. If diagnosis and treatment are delayed, acute adrenal insufficiency is associated with high morbidity and mortality.

P3-d1-1223 Autoimmune Endocrine Diseases 4

Difficulties in treatment of polyglandular autoimmune syndrome, type 1

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Background: Polyglandular autoimmune syndrome, type I or HAM syndrome (hypoparathyroidism, Addison's desease, moniliasis) is a very rare, autosomal recessive inheritance disorder and occurs in 90% between 3-5 years old or in early adolescence.
Objective: Presented 8y. 10m. old girl, from second normal pregnancy, first delivery, 20 days before term, weigh 2700 g and height 51 cm. Family history - brother with hypoparathyroidism, onychomycosis and alopecia areata, paternal grandfather with type 1 diabetes mellitus. This disease is from 3 years old, with tonic seizures, karpopedal cramps and hypocalcemia. Treatment started with 1,25 dihydroxy calciferol. One year later she had dystrophic nail changes, mucocutaneous candidiasis and alopecia areata. At the age of 4y. 9m. the girl was hospitalized in the Department of Endocrinology with pigmented skin, frequent abdominal pain, accompanied by vomiting and laboratory data for adrenal insufficiency. Cortineff and Hydrocortisone were added to the therapy. Six months later autoimmune thyroiditis with normal thyroid function was established. Since the age of 8 the child has suffered from pain in knee and ankle joints due to deposition of calcium in the joint capsule without cellular and humoral immunity deviations. The ultrasound of the kidneys showed bilateral increased parenchymal echogenicity with diffuse deposition of calcium. At 8 y. 9 m. she was admitted to the hospital with vomiting and abdominal pain. Laboratory findings showed hypercalcemia, acute renal insufficiency and ACTH > 2000 ng/l, which led to an increase in the dose of Hydrocortisone up to 20 mg per day.
Conclusions: Due to the five autoimmune disorders treatment is very difficult and requires frequent examinations and therapy adjustment.

P3-d1-1224 Bone, Growth Plate and Mineral Metabolism 7

Juvenile hypoparathyroidism

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Background: Hypoparathyroidism is a rare disease as well in children as in adults.
Objective and hypotheses: The aim of our study was to analyze etiologies and clinical characteristics of hypoparathyroidism in children.
Methods: It is a retrospective study concerning 10 children (5F/5M) in whom the diagnosis of hypoparathyroidism was made.
Results: Mean age at diagnosis was 13.66 ± 6.36 years but the mean age at the beginning of symptomatology was 9.42 ± 6.23 years with a diagnosis delay of 4.26 ± 5.10 years. Presenting symptoms were convulsions (50%), tetany (30%), reduction of visual acuity (10%) and paraesthesias (10%). On the biological level, mean calcemias were at 62.8 ± 14.29 mg/l, mean phosphoremias were at 80.6 ± 37.66 mg/l. Etiology was pseudohypoparathyroidism (30%), Sanjad Sakati syndrome (10%), autoimmune (10%), post thyroidectomy (10%) and idiopathic hypoparathyroidism (40%). Fahrs' syndrome was found in 30%, cataract was also noted in 30% of patients.
Conclusions: Hypoparathyroidism is rare and most often progress insidiously which can lead to the delay of diagnosis and serious complications, an early diagnosis by measuring calcemia in suspected patients may improve the prognosis of the disease.

P3-d1-1225 Bone, Growth Plate and Mineral Metabolism 7

Tumor-associated FGF-23 induced hypophosphatemic rickets in an 8-year-old boy

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Introduction: Tumor-associated Fibroblast Growth Factor 23 (FGF-23) induced hypophosphatemic osteomalacia has primarily been described in adults. On very rare occasions this entity may also be the cause of renal phosphate wasting and rickets in children, resulting from local production of phosphatonins by various benign and malignant mesenchymal tumors.
Case report: An eight year old boy was investigated for suspected unilateral painless limping. Radiographic evaluation showed a large and polylobulated cystic lesion in the left iliacal bone and acetabulum. Further typical clinical signs of rickets and the respective radiographic and laboratory signs including severe renal phosphate wasting were detected. Biopsy of the iliac lesion suggested a primary solitary bone cyst overlaid by a secondary solid aneurysmatic bone cyst. Laboratory findings, i.e. hypophosphatemia, renal tubular phosphate wasting, normal parathormone and normal calcitriol levels were not compatible with common forms of rickets in childhood. Tumor-induced rickets was therefore suspected and investigated with various methods, including PET-Scan and FGF-23 measurement in plasma. A causal lesion other than the iliac tumor or clearly abnormal FGF-23 could not be found. A complete curettage and stabilization of the acetabulum cyst were performed and local FGF-23 production was finally proven by immunohistochemistry in solid portions of the cyst. After surgery, tubular phosphate absorption normalized immediately and clinical and radiological signs of rickets quickly resolved without any further need for substitution of phosphate or other interventions.
Conclusion: Tumor-induced hypophosphatemic rickets have only rarely been described in children. Nevertheless this diagnosis has to be considered in paediatric patients who present with acquired hypophosphatemic rickets beyond infancy.

P3-d1-1226 Bone, Growth Plate and Mineral Metabolism 7

A 5-year-old boy with massive osteolysis and hypophosphatemic rickets

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Background: Massive osteolysis is a rare disorder of the musculo-skeletal system. Hypophosphatemic rickets is known to be caused by elevated serum fibroblast growth factor 23 (FGF23). McCune-Albright syndrome (MAS) is characterized by the clinical triad of precocious puberty, cafe-au-lait skin lesions, and fibrous dysplasia of bone. A subset of patients with MAS presented hypophosphatemic rickets and fibrous dysplasia.
Case presentation: We report a 5-year-old boy with massive osteolysis and hypophosphatemic rickets. At 1 year of age, he presented with gait disturbance and genu varum. At 2 years of age, his parents consulted with orthopedists. Radiographic examination revealed cupping and fraying of the metaphyseal regions, suggestive of rickets, and osteolytic lesions at both arms and upper left femur. Laboratory examinations revealed hypophosphatemia (2.0-2.5 mg/dL, reference 4.5-6.2) and elevated serum FGF23 (73 pg/mL, reference 10-50). The diagnosis of MAS was not confirmed by bone biopsy. We initiated alfacalcidol and phosphate supplementation. At 4 years of age, other osteolytic lesions appeared at pelvis and skull. He received alfacalcidol at doses up to 1.0 µg/day as well as phosphorus 580 mg/day with no evidence of radiographic or biochemical healing. Tumor-induced hypophosphatemic rickets was excluded by computed tomography, magnetic resonance imaging, scintigraphy and selective venous sampling for FGF23. Octreotide treatment did not improve hypophosphatemia. Repeated bone biopsy revealed nonspecific findings. At 5 years of age, remission gradually occurred. No activating mutations in GNAS were detected in his leukocytes. The etiology remained to be identified.
Conclusion: Our observation may suggest that a full skeletal X-ray survey is needed when we encounter patients with hypophosphatemic rickets.

P3-d1-1227 Bone, Growth Plate and Mineral Metabolism 7

Acute vitamin D intoxication in three children: unproven manufacturing error of unique multivitamin preparation

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Background: Vitamin D intoxication usually occurs as a result of inappropriate use of vitamin D preparations and can lead to life threatening hypercalcemia.
Objective and hypotheses: Even though improper use of vitamin D supplements may lead to vitamin D intoxication, to our knowledge there is no reported vitamin D intoxication due to manufacturing errors of supplements throughout childhood. We present three cases of vitamin D toxicity due to suspicious manufacturing errors of prescribed multivitamin supplements.
Method: The vitamin D level of the multivitamin preparation was studied using High Performance Liquid chromatography (HPLC) method following extraction process.
Results: All of the cases came with hypercalcemia symptoms and had classical laboratory findings characterized by hypercalcemia, hypercalciuria, low levels of parathyroid hormone. Very high serum 25(OH) vitamin D levels (> 150 ng/mL) indicated vitamin D intoxication. The vitamin D level of the prescribed multivitamin preparation was found to contain very low level of vitamin D (10 IU/5 mL). Although vitamin D content of preparations were not detected high, as preparations used by patients and examined at the laboratory were not the same, it was considered that preparations used by patients might have higher levels of vitamin D due to manufacturing errors at that time interval, which might have led to intoxication.
Conclusions: We underline that
(i) vitamin D supplement should be prescribed in patients only when rickets is proven based on clinical and laboratory findings,
(ii) multivitamin preparations should not be used for vitamin D treatment and
(iii) the patients unnecessarily treated with vitamin D should be evaluated for intoxication.

P3-d1-1228 Bone, Growth Plate and Mineral Metabolism 7

The management of osteogenesis imperfecta in the South-West part of Romania in different ethnic groups

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Background: Osteogenesis imperfecta (OI) is an inheritead disorders of type I collagen, characterized by bone fragility, blue sclerae, hearing lost and short statures.
Objective: The authors aimed to study the effects of the anti-resorptive agents in pediatric patients with OI on different ethnic groups.
Methods: The study lot comprised pediatric patients admitted to Children Hospital, Timisoara, Romania with OI and treated with biphosphonates. Medical charts, phospho-calcic metabolism, bone turnover markers and imagistic evaluations were analyzed before and after treatment.
Results: We managed the treatment of 12 patients (5 boys, 4 roma children) diagnosed with OI during the last 5 years. Their aged ranged between 4 months and 21 years old. According to Sillence classification, 50% of patients were classified as type I, 33.34% as type IV and 16.66% as type III. On clinical examination, no blue sclaera was described and the number of the fractures varied between 3 and 39 per patient. Femur (43%) and tibia (31%) bones were frequent affected. No side effects were reported after biphosphonates (1 mg/kg/day for 3 days every 3-4 months) and vitamin D (1000 UI/day) treatment. We could not find "zebra lines" at X-rays in patients with this treatment for 2-3 years. Reductions in bone alkaline phosphatase and in number of fractures after biphosphonates were reported. An improvement of Z score at DXA examinations in 2 children older than 12 years (from -2.7 to -2.1) and significant enhancement of the mobility were observed. Surgical treatment (pinning; intramedullary nailing and plating) were performed in 3 children (2 roma ones). GH therapy was associated in one roma patient with severe short stature with height velocity rate of 0.34 cm/month.
Conclusions: Bisphosphonates treatment was beneficial in children with OI, increasing bone mineral density and reducing the fracture rate. No adverse effects were reported. No ethnical characteristics were encountered.

P3-d1-1229 Bone, Growth Plate and Mineral Metabolism 7

Evaluation of two different pamidronate treatment protocols in children with osteogenesis imperfecta

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Background: Osteogenesis imperfecta is an inherited disorder of connective tissue. Children with this condition suffer from recurrent fractures, deformities, osteoporosis and pain. Over the recent years, pamidronate became the standard treatment choice. However the optimal dose and interval have not been defined yet.
Objective and hypotheses: In this study, we aimed to evaluate two different protocols of pamidronate by clinical, biochemical, and radiological findings in children with osteogenesis imperfecta.
Methods: 12 patients aged 42.3 ± 37.4 months were studied. At the beginning patients had received pamidronate infusion at a dose of 1.5 mg/kg/day

once, every two months with duration of 23.5 ± 9.0 months (first protocol), than switched to a dose of 1mg/kg/day for three consecutive days, every three months with duration of 18.5 ± 5.1 months (second protocol). Ambulation scores were determined before and after each protocol. The bone mineral density Z-score was evaluated yearly.
Results: Annual fracture rate decreased from 6.3 ± 5.5 to 1.1 ± 1.3 ($p< 0.001$) in the first and from 1.1 ± 1.3 to 0.0 ± 0.0 ($p< 0.001$) in the second protocol. Bone mineral density Z-scores increased from -3.9 ± -1.4 to -2.5 ± -1.3 ($p< 0.05$) in the first, and from -2.5 ± -1.3 ± -1.2 ± -1.1 ($p< 0.05$) in the second protocol. Ambulation scores were improved in both protocols.
Conclusions: Our study demonstrated that higher yearly doses in 3 consecutive day administration of pamidronate did not provide any additional beneficial effects. Furthermore, higher doses of treatment and longer duration of hospitalization led to the loss of school hours and work hours of parents and was more costly.

P3-d1-1230 Bone, Growth Plate and Mineral Metabolism 7

Caffey disease with R836C *COL1A1* mutation: a case report

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Introduction: Caffey disease, or infantile cortical hyperostosis, is a benign self-limiting disease, characterized by irritability with restlessness, soft tissue swelling, and massive subperiosteal new bone formation in multiple bones of the skeleton. Its pathogenes is ambiguous, no cause has been proven to date. Here, we report the case of a Chinese boy with caffey disease, and carried out genetic analysis. This is the first family case of caffey disease performed genetic analysis in China.
Case study: A 6-month-old Chinese boy was referred to our out-patient because of right upper limb and lower limbs swelling with tenderness for 3 months. Besides limbs swelling, examination revealed diffuse, immobile swelling without tenderness over right mandible. There was no fever, skin abnormal, or lymph nodal enlargement. No trauma, drug intake or family history was recorded. Laboratory tests showed increase in white cell count, C-reactive protein concentration, and alkaline phosphatase level. X-ray of bones confirmed that there was massive subperiosteal new bone formation over bilateral femoral and tibia, right radius, and right mandible. Then the boy was followed up every 3 months without special drug treatment, and he completely recovered one year later, which confirmed the diagnosis of caffey disease. DNA sequence analysis of exon 41 of *COL1A1* disclosed a heterozygous mutation (c.3040C > T, p.R836C) in the affected boy. His father was normal, while his mother carried the same mutation.
Conclusion: Our result supported that caffey disease is an incomplete penetrance disorder, caused by *COL1A1* mutation. The hot-spot mutation is R836C.

P3-d1-1231 Bone, Growth Plate and Mineral Metabolism 7

An unusual presentation of PHEX mutated X-linked hypophosphatemic rickets in a child

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Introduction: X - linked hypophosphatemic rickets (XLHR) is a rare disease caused by mutation in PHEX gene. XLHR usually presents with short stature, abnormal gait and skeletal manifestations of rickets. We here report on an unusual case of XLHR presented with bilateral proptosis and misdiagnosed as bilateral optic glioma.
Case study: A 5 year old girl presented with a leg bowing noticed at the age of 1 year and a progressive eye protrusion started at 3 years of age. No history of headaches, visual impairment or symptoms suggestive of hyperthyroidism. She passed through normal development apart from mild delay of motor milestones. She received multiple courses of vitamin D3 without improvement. MRI of brain, done in the referring hospital reported bilateral optic nerve sheath ectasia and bilateral glioma. Clinical examination confirms bilateral moderate proptosis in the right eye more than the left with intact visual acuity and eye movements. Fundoscopy showed a pale optic disc. There were no signs suggestive of hyperthyroidism. Height and weight were at 10th centile. No skeletal signs of rickets observed apart from bowing of legs and waddling gait. Laboratory investigations showed normal serum corrected calcium of 2.3 mmol/l (N= 2.1-2.55), low phosphorus 0.84 mmol/l (N= 0.87-1.45) and ALP of, 486 U/L (N= 50-136). PTH, 25 hydroxyvitamin D, 1, 25 dihydroxyVitamin D, TSH and T4 were normal. Skeletal survey showed generalized osteopenia with no specific signs of rickets. Molecular genetic analysis of PHEX gene Shows heterozygous mutation c.1735G>A (p.Gly579Arg. The patient was commenced on high dose of alfacalcidol and oral phosphate. Review of the MRI brain confirms presence of bilateral optic nerve sheath ectasia that mimics optic glioma.
Conclusions: This report highlights the rare association of bilateral proptosis and XLHR. This should be considered in the differential diagnosis of unexplained proptosis.

P3-d1-1232 Bone, Growth Plate and Mineral Metabolism 7

Novel PHEX gene mutation in a Korean family with X-linked hypophosphatemic rickets

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Background: X-linked hypophosphatemia (XLH), the most prevalent heritable form of rickets, is a dominant disorder that is characterized by renal phosphate wasting with hypophosphatemia, abnormal vitamin D and parathyroid hormone metabolism, defective bone mineralization, short stature, and rachitic manifestations. The related gene with inactivating mutations associated with XLH has been identified as the phosphate-regulating endopeptidase (PHEX), which is a phosphate-regulating gene with homologies to endopeptidases on the X chromosome.
Methods: We investigated a Korean family who exhibited typical features of XLH, and in whom mutational analysis using PCR and sequencing was performed.
Results: A 14-yr-old female was admitted to the outpatient clinic reporting short stature. Physical examination revealed deformities in the lower extremities including bowing of the legs. Her mother and grandmother also had a history of vitamin D-resistant rickets, but they did not receive treatment. Laboratory analyses of serum revealed the following values: inorganic phosphate 1.9 mg/dl, 25-hydroxyvitamin D3 4.15 ng/ml, alkaline phosphatase 843 U/L. The maximum tubular capacity of phosphate per unit volume of glomerular filtrate was 1.67 mg/dl. Radiologic findings showed diffuse bony contour changes with osteoporotic changes and notable bowing of the tibiae and fibulae. Direct nucleotide sequencing revealed a heterozygous mutation in exon 20 [c.2061T>A (p.Ser687Arg)], which, to the best of our knowledge, has not been reported yet. The same mutation was found in her mother and grandmother, also. The patient was treated with 2,000 mg oral phosphate and 0.5 g calcitriol.
Conclusions: Our report identifies a novel mutation in the PHEX gene, which might be the cause for XLH in this Korean family. Our data are useful for understanding the genetic basis of Korean patients with XLH and contributing to the decipherment of the pathogenetic pathways of XLH.

P3-d1-1233 Bone, Growth Plate and Mineral Metabolism 7

Bilateral slipped capital femoral epiphysis (SCFE) with vitamin D deficiency and extremely high levels of parathyroid hormone in a 7-year-old boy

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Introduction: SCFE is relatively common disorder in childhood especially among obese boys. Although vit D deficiency as a cause of SCFE have been postulated, very few cases have been described.
Case study: 7 year old african american boy with normal BMI was admited for difficulty and pain with walking. He was diagnosed with bilateral SCFE and underwent b/l hip surgery with pin placement. Work up for Ca/vit D metabolism disorders was preformed. Pt had normal BUN and creatinine, vit D

25OH was 9 ng/ml, vit D1,25 OH of 16 pg/ml, serum Ca of 8.4 mg/dl, iCa of 1.35 mmol/L, phos of 6.5 mg/dl, alk phos 431 U/L, iPTH 657 pg/**ml**. Skeletal survey showed osteomalacia with features of secondary hyperparathyroidism. Pt was started on vit D (Drisdol 8000IU daily) for 12 weeks. Family however had issues with compliance and pt was lost to follow up for 8 month. At the next follow up pt had normal BUN and creatinine, vit D 25OH of 12.8 ng/ml, vit D1,25 OH of 55 pg/ml, serum Ca of 7.7mg/dl, iCa of 1.2 mmol/L, phos of 5.4 mg/dl, alk phos of 325 U/L, iPTH 1151pg/ml. Noncompliance with vit D was thought to cause abnormal values and patient underwent treatment with vit D 50,000 IU weekly po for 12 weeks observed by staff in the clinic. DEXA scan was obtained at that time showed osteopenia of the lumbar spine with Z-score of -1.5. Pt underwent 2 additional hip surgeries with pin revisions. Now vit D 25OH was 16.7 ng/ml, vit D1,25 OH of 49 pg/ml, serum Ca of 8.4 mg/dl, iCa 1.1 mmol/L, phos of 5.2 mg/dl, alk phos 369U/L, iPTH 1972pg/ml. At that time treament was changed to Calcitriol 0.25mcg bid, and elemental Ca of 50mg/kg/daily. In 3 month Vit D 25OH was 18 ng/ml, vit D1,25OH of 59 pg/ml, total Ca of 8.9 mg/dl, normal phos, iPTH of 403 pg/ml. Dexa scan showed mild improvement.

Conclusion: This is unusual case of SCFE possibly due to combination of vit D defficiency and pseudohypoparathyroidism type IB as our patient has no signs of renal insuficiency and normal phenotypical appearance.

P3-d1-1234 Bone, Growth Plate and Mineral Metabolism 7

Bone mineral density in Turner syndrome

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Turner syndrome (TS) is an important cause of short stature in girls and primary amenorrhea in young women. The condition occurs in approximately 1 in every 2000 live female births (2). Affected girls may also encounter a wide range of problems including decreased bone mineral density.

Aim: We aim to describe the bone mineral density and to determine its relation to puberty and age in girls with TS. Management of abnormal bone density will also be discussed.

Methodology: Girls with TS, aged over 12 years, are invited to participate in the study. All participants underwent auxology, pubertal assessment, DXA scan, bone age evaluation and blood tests.

Results: In 32 girls with TS (mean (SD) age 16.7 (2.61) years). Structural X abnormalities with or without mosiacism was the most common chromosomal abnormalities (14/32 (43.75%). Mean (SD) height (cm) was 148.26 (9.01). Girls with TS have lower Bone Mineral Apparent Density (BMAD) values at trabecular bone, compared with the age-matched general population. BMAD values were positively and significantly associated with breast Tanner stages and post-menarcheal status. However, there was no significant difference in DXA results between individuals with spontaneous and those with induced puberty. No significant association between BMAD values and growth hormone or oestrogen therapy was found.

Conclusion: Girls with TS have lower BMAD values at trabecular bones, compared age and sex-matched general population. There was significant association between BMAD values and pubertal development, being higher in postmenarche girls than those with breast Tanner stage 2 or more without menarche.

P3-d1-1235 Bone, Growth Plate and Mineral Metabolism 7

Cinacalcet in management of hypophosphatemic rickets one week after treatment

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Background: Hypophosphotemic rickets (HR) results in decrease reabsorption of phosphrus (PO) by the proximal renal tubule along with inhibition of 1α-hydroxlase leading to low levels of 1,25 (OH)2-vitamin D. Standard treatment includes PO replacement and 1,25 (OH)2-vitamin D. Complications to this therapy include renal insufficiency and secondary hyperparathyroidism. Calcimimetics modulate the calcium sensing receptor (CaR) resulting in decrease PTH secretion.

Design: Two cases of patients with HR managed with PO replacement and calcitriol, but PO evels were hard to normalize. Cinacalcet at 30 mg twice daily was started, and serum measurements of calcium, PO, and PTH were compared before starting and after 1weekand 3 months of treatment.

Results:

Case 1 is an 11yo boy who presented at 7yrs of age with history of leg bowing, sleep apnea due to facial bone malformation, dental caries, and bone pain. X-linked HR was confirmed with missense mutation of PHEX gene. On calcitriol 1.5mcg daily and PO 30mg/kg/day serum PO was never above 2.5mg/dL, while PTH was 70pg/dL and Calcium of 9.6mg/dL. One week after starting cinacalcet, PO improved to 3.5 along with a decrease in PTH to 25 and calcium of 9.

Case 2 is of a 6yo girl who presented at 2yrs of age with leg bowing, frontal bossing, and bone pain. Genetic analysis for cause of HR pending. Patient was on calcitriol 1mcg daily along with PO 18mg/kg/day. Cinacalcet was started and one week later PO improved from 2.6 to 3.5, PTH went from 20 to 12, while calcium changed from 9.3 to 9.1. 3 months later PO remained normal 4.5 mg/dl, Ca while decreased to 7.8mg/dl and PTH to < 3 mg/dl. Cinacalcet dose was decreased.

Conclusion: Addition of cinacelcet to PO and Calcitriol had an immediate effect on decreasing PO replacement requirements along with reduction in PTH levels. Cinacalcet can play a quick and significant role in better managing HR.

P3-d2-1236 Bone, Growth Plate and Mineral Metabolism 8

A rare case of severe hypocalcaemia in an infant

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Background: Malignant infantile osteopetrosis (MIOP) is a rare autosomal recessive bone disease, characterized by reduced or dysregulated osteoclastic activity and increased bone mass. Major consequences include bone marrow failure and nerve compression. Rickets is a paradoxical feature of osteopetrosis resulting from inability to maintain a normal calcium-phosphorus balance in the extracellular fluid. It is suggested that although the calcium balance is positive in these patients,the skeleton sequesters the calcium because of osteoclastic dysfunction so that the serum level of calcium paradoxically may decrease.

Methods: Case report of a 3 months old boy admitted to the clinic for seizures due to severe hypocalcemia. A dysmorphyc phenotype was noticed. Based on the presence of anemia, hypocalcemia, hepatosplenomegaly, failure to thrive, mental retardation, ventriculomegaly, optic nerve atrophy and the typical radiological images diagnose of MIOP complicated by rickets-osteopetrorickets was established. High doses of calcium(50 mg/kg/d) and active vitamin D (calcitriol-0,3 ug/kg/d)) were given with a slow biological improvement. After 1 month of treatment vitamin D level normalized; PTH remained elevated.

Conclusions: The association of osteopetrosis complicated by rickets led in our case to severe hypocalcemia. High dose of vitamin D are needed to improve the osteoclastic activity. The prognosis in this case remains very poor, death occurs in the first decade of life as a complication of bone marrow supression.

P3-d2-1237 Bone, Growth Plate and Mineral Metabolism 8

Cardiac evaluation of paediatric patients with hypophosphatemic rickets

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Background: The majority of patients with hypophosphatemic rickets show elevated serum fibroblast growth factor 23 (FGF23) levels. Patients with chronic kidney disease also have elevated FGF23 concentrations, which is

frequently accompanied by left ventricular hypertrophy (LVH). While several studies suggest that FGF23 might directly induce LVH, few reports have investigated the relationship between hypophosphatemic rickets and LVH.
Objective: The goal of this study was to evaluate cardiac function and LVH in pediatric patients with hypophosphatemic rickets.
Methods: Five patients (two males and three females) with hypophosphatemic rickets were studied. The mean age of the subjects was 7.8 year (range, 3-11 years), and all patients were receiving alfacalcidol (0.05-0.16 μg/kg/day) and phosphate (39-51 mg/kg/day). Serum FGF23 concentrations were measured in three of five subjects. All subjects underwent electrocardiography and chest x-ray examinations. Further, two-dimensional trans-thoracic echocardiography was performed to calculate the left ventricular mass (LVM) using the area/length method. LVM was compared with the predicted LVM, which was calculated as follows: 65 × body surface area$^{1.25}$ + 0.2. Relative wall thickness (RWT) was calculated as: (2 × posterior wall thickness at end-diastole) × left ventricular internal dimension at end-diastole^{-1}.
Results: FGF23 concentrations were elevated in all three subjects (86, 311, and 415 pg/ml). All subjects showed normal electrocardiography, normal cardiothoracic ratio, and normal cardiac function. The mean LVM was 55.0 ± 17.6 g (range, 34.9-74.6 g), and the results of LVM were between 89.9% and 103.1% of the predicted LVM. The mean RWT was 0.32 ± 0.07 (range, 0.23-0.40), and no subjects showed abnormally increased RWT (> 0.42). These results indicate that the subjects in this study had normal left ventricular geometry.
Conclusions: Pre-teen patients with hypophosphatemic rickets do not appear to have LVH.

P3-d2-1238 Bone, Growth Plate and Mineral Metabolism 8

Vitamin D deficiency and secondary hyperparathyroidism among schoolchildren of Ukraine

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Background: Vitamin D deficiency has various causes, including limitations in sunlight exposure (type of clothing, sunscreen usage, indoor activity), seasonal geographic latitude and altitude, atmospheric pollution, diet, and ageing.
Objective and hypotheses: The aim of the work was to determine the frequency of vitamin D deficiency and secondary hyperparathyroidism among Ukrainian schoolchildren.
Methods: There were examined 304 children aged 10-18 years. The boys consisted 55.0 %. The average age of boys was 12.9±0.2 and girls - 12.4±0.2 yr. old. The study was performed within two months - October and November 2011, to exclude the influence of seasonal factors on the level of 25(OH) D. Researches included blood chemistry, 25(OH)D and intact parathyroid hormone (iPTH) in plasma were determined by Elecsys 2010. Also, it was evaluated the average content of calcium and vitamin D in the diet form the products consumption frequency questionnaire.
Results: Vitamin D deficiency was founded in 92.2 % of schoolchildren, and vitamin D insufficiency was diagnosed in 6.1 % of cases. The average level of 25(OH)D in the blood serum of children reached puberty was (28,67 ± 1,10) nmol/l and did not significantly lower compared with its level in the surveyed children aged 10 -11 years ((32,47 ± 2,30) nmol/l) and aged 16-17 years ((33,59 ± 3,56) nmol/l). BMI didn't influenced on the level of 25(OH)D in blood serum. Secondary hyperparathyroidism was verified in 0.9 % of children. The average level of consumption of calcium and vitamin D in children was below recommended data, and consisted (Me 649 [488.7; 691.86]) mg/day for calcium and (Me 68.69 [58.45; 691,86] мг/д)1 IU/day for vitamin D.
Conclusions: High level of vitamin D deficiency (92.2 %), secondary hyperparathyroidism (0.9 %) make doctors to research the effective methods of treatment and prophylactics of revealed disorders.

P3-d2-1239 Bone, Growth Plate and Mineral Metabolism 8

Urinary calcium to creatinine ratio is valuable in detecting secondary hyperparathyroidism in patients with abnormal vitamin D metabolism

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Background: Hypocalcemia is one of the most important complications in patients with abnormal vitamin D metabolism throughout life. When serum calcium decreases, intact-PTH (iPTH) is secreted to maintain serum calcium levels. In the kidney, increased iPTH induces enhancement of calcium reabsorption, therefore urinary calcium excretion is decreased. It is difficult to predict latent secondary hyperparathyroidism only by serum calcium levels in compensatory normocalcemic state. Thus, the measurement of iPTH is used for the most sensitive marker for hypocalcemia.
Objective and hypotheses: Based on the fact that the relationship between PTH secretion and renal reabsorption of calcium shows positive correlation, we hypothesize that the relationship between serum iPTH and the level of urinary calcium to creatinine ratio (U-Ca/Cr), which is much easier to assess, would show negative correlation. The objective of this study was to determine whether U-Ca/Cr is valuable as with iPTH in detecting secondary hyperparathyroidism in patients with abnormal vitamin D metabolism.
Methods: Two adolescent brothers and an adult man, who were diagnosed as vitamin D dependent rickets type 1A (VDDR1A) with null mutation of CYP27b1, which encodes 1-alpha-hydroxylase of 25-hydroxy vitamin D, were investigated. Their data of serum iPTH and U-Ca/Cr were obtained and analyzed to estimate the relationship, and were compared to those of five patients who were diagnosed as vitamin D deficiency (VDD) at more than two years old.
Results: The levels of U-Ca/Cr could detect secondary hyperparathyroidism. The relationship between U-Ca/Cr and iPTH in VDDR1A patients showed inverse correlation and that in VDD patients were represented as reverse sigmoid curve. When U-Ca/Cr decreased less than 0.1, serum iPTH was increased even in normocalcemic state.
Conclusion: Cut-off ratio of U-Ca/Cr less than 0.1 is valuable in detecting secondary hyperparathyroidism in patients with VDDR1A and VDD.

P3-d2-1240 Bone, Growth Plate and Mineral Metabolism 8

Infantile malignant osteopetrosis: case report

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Background: Osteopetrosis is a rare inherited bone disease caused in each of its forms by defective osteoclast function which results in generalized increase in skeletal density. Malignant infantile osteopetrosis form (MIOP) is an autosomal recessive disease characterised by hematological difficulties, hepatosplenomegaly, infections, pathological fractures, and cranial nerve compression leading to blindness and deafness.
Objective and hypotheses: We report a 5 month old infant with the malignant form of osteopetrosis. The patient was hospitalized due to failure to thrive, growth retardation, marked hepatosplenomegaly, and severe bone deformities.
Methods: The diagnosis was based on physical findings, haematological investigations, and radiographic skeletal features.
Results: The examinations revealed severe bone marrow failure resulting in anemia, trombocitopenia, and massive hepatosplenomegaly due to compensatory extramedullary hematopoesis. Radiographic diagnostic findings showed generalized increase in bone desity, with defective metaphyseal modelling, and "bone-in-bone" appereance most marked in the proximal femora and pelvis. Because bone marrow transplant is the only curative treatment for patients with malignant infantile osteopetrosis, the infant was refered to a bone

marrow transplantation center.
Conclusions: Malignant infantile osteopetrosis is a rare cause of hepatosplenomegaly, and bone deformities. Skeletal roentgenograms are of clinical importance in the diagnosis.

P3-d2-1241 Bone, Growth Plate and Mineral Metabolism 8

Vitamin D deficiency in girls with Turner syndrome

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Background: Most patients with Turner syndrome (TS) have no gonadal function and are deficient in female sex steroid from early childhood. Beside gonadal insufficient the cardinal stigmata of TS are growth retardation with reduced final height, infertility and a number of congenital malformations. Adolescents and young adults with TS have decrease bone mineral density (BMD) with risk of osteoporosis and fracture that may be due to the chromosomal abnormality or missing SHOX gene expression, lack of estrogen, testosterone and hyperthyroidism. Just few studies have interest to the vitamin D statue and its role in the genesis of decrease bone density in young girls with TS.
Cases studied: We report five cases of vitamin D deficiency in young girls with TS. We examined 1, 25 -Dihydroxy vitamin D, TSH, FT4, Oestradiol in adolescents, celiac serology, bone mineral density (by DXA) and caryotype. Results are represented in the following table:

Patients	Age	Height (cm) (SDS)	TSH (µUI/ml)	FT4 (pg/ml)	Oestradiol (pmol/l)	Vitamin D (ng/ml)	celiac serology	BMD by DXA
Case 1	18	144(-3)	2,6	14,2	8,29	13,25	negative	Osteoporosis
Case 2	15	135(-4,5)	4,1	11,1	2,4	18	negative	Osteoporosis
Case 3	3	83(-2)	1,68	7,27	-	12,56	negative	Normal
Case 4	4	96(-1)	2,06	16,7	-	14,20	negative	Osteopenia
Case 5	3	88(-1)	2,75	15	-	7,23	negative	Osteopenia

[Patients characteristics.]

Caryotype of cases 1,2,4 was: 45X/46XX,and 45X0 for Cases 3-5.
Conclusions: Low provision of vitamin D in girls with TS may participate to low BMD especially in cortical bones. The vitamin D deficiency in TS may be due to altered renal vitamin D metabolism in response to physiological stimulus ,malabsorbtion due to celiac disease could also participate to its genesis. It's important to evaluate Vitamine D statue in girls with TS despite their young age, because the correction of hypovitaminose D may improve their BMD and reduce the risk of fracture.

P3-d2-1242 Bone, Growth Plate and Mineral Metabolism 8

Vitamin D status in Irish children and adolescents: value of fortification and supplementation

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Background: Ireland's northerly latitude places the population at risk of vitamin D deficiency. Peak bone mass accrual may not be achieved in children and adolescents with vitamin D deficiency. Suboptimal vitamin D levels have been associated with several adverse health outcomes.
Objective: We sought to assess vitamin D status and its determinants in healthy Irish children.
Methods: We conducted a prospective cross-sectional study over a 12 month period from July 2010-July 2011. Healthy children attending the hospital for elective procedures were recruited. Each patient enrolled completed a questionnaire on vitamin D intake from diet, vitamin D supplementation and sun exposure. Serum 25-hydroxyvitamin D(25OHD), parathyroid hormone and bone profile were measured.
Results: We studied 252 children(162 girls); the age range was 1.0-17.2 years. The mean(SD) serum 25OHD was 47(38.5) nmol/L. According to Institute of Medicine (IOM) guidelines on vitamin D status, 21.9% had serum 25OHD levels below 30 nmol/L, 32.7% were in the range of in adequacy (30-50 nmol/L), and 45.4% had levels above 50 nmol/L. Significant association with vitamin D status were noted for age under 4 years, use of infant formula feed, use of vitamin D supplementation, and summer season.Independent determinants of vitamin D status (25OHD > 50 nmol/L) according to multiple binary logistic regression analysis were as follows:infant formula feed(OR=3.9, 95%CI=1.1-13.6);taking vitamin D supplements(OR=3.58, 95%CI=1.6-7.6]);blood sampling from April-to-September(OR=3.5, 95%CI=1.9-6.7).
Conclusions: More than half of the children in this study had serum 25OHD levels below the threshold for sufficiency.Given the benefit in our study of better vitamin D status by augmented oral vitamin D intake (by formula feed or by supplementation), national policies of fortification and targeted supplementation in at-risk groups should be considered.

P3-d2-1243 Bone, Growth Plate and Mineral Metabolism 8

Aetiology of hypoparathyroidism in a region of North Africa with high consanguinity

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Background: Parathormone (PTH) deficiency may acquired or more rarely, congenital. We have observed an unsual prevalence of rare, syndromic congenital causes of hypoparathyroidism in our centre.
Objective and hypotheses: To determine the clinical features and evolution of childhood hypoparathyroidism in our centre.
Methods: Longitudina retrospective study of patients diagnosed with hypoparathyroidism on the basis of persistent hypocalcemia, normal alkaline phosphatase and low PTH.
Results: 6 cases, all males, were identified between 2003 and 2009. Presentation was with seizures in all cases at median(range) 50 (30-120) days in 5 infants and at 15 years in oneboy. Median (range) calcium levels were 60.3 (N:86-90mg/l), phosphate 52.4 mg/l (N:45-60 mg/l). Aetiology was unkown in 2 infants (positive consanguinity in one) sanjad-sakati syndromein another (consanguineous family) with death at 1 year of age, Kenny-Caffey syndrome in a fourth and familial hypoparathyroidism in the fifth infant, with a history of male sibling death from hypoparathyroidism at 40 days. The 15-year-old boy Fahr syndrome. Treatmentwas with 1 alpha Vit 3 1-3 ug daily in all cases with calcium 500-1000 mg/m^2 in 3 cases. Three of the cases have developed nephrocalcinosis.
Conclusions: We confirm an unsual pattern of complex syndromic causes of hypoparathyroidism in our centre, related to high consanguinity rates (estimated 38% in Algeria). The true prevalence of syndromic hypoparathyroidism is likely to be higher than our figures suggest, due to some cases dying undiagnosed. Our experience underlines the need to estabilish links with centres wich are able to carry out the necessary genetic analyses in our patients.

P3-d2-1244 Bone, Growth Plate and Mineral Metabolism 8

Cinacalcet has a limited effect in hyperparathyroidism secondary to X-linked hypophosphatemic rickets: a case report

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Background: X-linked hypophosphatemic rickets (XLHR) is the most common form of inherited rickets. Conventional therapy with oral activated vitamin D and phosphate can lead to secondary or tertiary hyperparathyroidism (HPT). Recently, the calcimimetic drug cinacalcet was reported to be effective in secondary HPT in dialysis patients. Calcimimetics can be used to manage HPT through their action on the cell surface calcium-sensing receptor of the parathyroid.
Objective: To describe a 20-year-old man with XLHR complicated with tertiary HPT who was treated with cinacalcet.

Case report: He was the first child of nonconsanguineous parents. Family history was unremarkable. At the age of 22 months, he was diagnosed with hypophosphatemic rickets based on rachitic change in Xp, low serum phosphate levels, and low reabsorption of phosphate. At the age of 19 years, DNA analysis revealed a c.2044C>T nonsense mutation in exon 20 of the *PHEX* gene as a mosaic. He had been treated with activated vitamin D and phosphate since diagnosis. Serum intact PTH (iPTH) levels had tended to increase from the age of 16 years. He was diagnosed with tertiary HPT because the iPTH (300-360 pg/mL) and serum calcium (11.1-12.2 mg/dL) levels remained high despite interrupting the therapy, and he had moderate renal dysfunction caused by long-term abnormal mineralization. We started cinacalcet to decrease the iPTH and serum calcium levels. However, he required a total parathyroidectomy with autotransplantation at the age of 20 years because of failed maximized medical management. The pathology showed hyperplasia in each isolated parathyroid gland.
Conclusions: Studies have reported that cinacalcet is effective in patients with marked parathyroid hyperplasia and can be an alternative to parathyroidectomy for severe secondary HPT. However, our case suggests that cinacalcet is ineffective for advanced HPT secondary to XLHR.

P3-d2-1245 Bone, Growth Plate and Mineral Metabolism 8

Hungry bone treatment in one child with malignant hypercalcaemia due to pareneoplastic syndrome in acute lymphoid leukaemia

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Background: Seriously Hypercalcemia it's a very rare in pediatric settings-Usually it's due to primary hyperparatyroidism or it's secudnary to abnormalities in the levels of 1,25 dyhydroxi vitamin D or PTH related hormone in the context of hematologic malignities or granulomatose disease. The treatment of the primary cause it's the rule, but some times the diagnosis it's delayed in paraneoplastic tumoral presentations. When the response to hemodialysis and hydratation it's bad, bisphosphonate are the treeatment choice if the vitamin D levels are normal.
Objective and hypotheses: We presented the optimal response to a low dose of Zolendronate in a child with refractorious hypercalcemia with posterior hungry bone which was treated whit hig dose of oral and parenteral calcium and oral phosphate 2% solution and calcitriol, after many studioes the second myelogram shown Acute Leukemia.
We shown the severe descompensation after the zolendronate but also te adequiate response a adjust of phosphate and calium delivery until de resolution of the clinical case.
Conclusions: In cases of refractory hypercalcemia, bisphosp'honates may be used with extreme caution due to the posibility of supresion of celular production of rPTH of celular cells and the lacunae may be development hungry bone, in similar fashion like the primary hyperparathyroidism when vitamin D deficiency it's assosiated, the suspect and early follow up may be critical for give protection of cardiovascular symptoms of hypocalcemia and hypocalcemia in tgis critical patients.

P3-d2-1246 Bone, Growth Plate and Mineral Metabolism 8

Refractory hypocalcaemia induced by influenza virus in primary hypoparathyroidism

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Background: Hypocalcaemia presents as an acute medical emergency or a chronic disorder difficult to control.
The maintenance of normal serum calcium concentration depends on the balanced effects of parathyroid hormone (PTH), vitamin D, calcitonin.
In primary hypoparathyroidism, PTH secretion is decreased or absent, with the request of a daily replacement treatment with calcium and vitamin D.
Methods: We present the case of a 14-year-old boy, with known well treated idiopathic hypoparathyroidism. He was treated with calcium and vitamin D with an adequate control of calcium levels. Fever (> 39°C), myalgia and muscular spasm occurred and Influenza virus infection was confirmed by nasal specimen. He showed severe and refractory hypocalcaemia (6,5 mg/dl), with mild ECG alterations, normal creatine kinase values, treated with intravenous calcium gluconate infusion, vitamin D.
Results: Refractory hypocalcaemia persisted with recovery only after gradual resolution of fever.
Conclusions: This was the second time that influenza infection caused symptomatic severe hypocalcaemia in this patient.
Actually the influenza vaccine is recommended for this patient, to prevent further recurrence of refractory hypocalcaemia in course of influenza infection.

P3-d2-1247 Bone, Growth Plate and Mineral Metabolism 8

Pseudohypoparathyroidism: case report in pediatrics

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Background: Pseudohypoparathyroidismo is a group of disease transmitted as autosomic dominant and characterized by hypocalcemia, hyperphosfhatemia, elevated serum PTH and decresed tissue sensitivity to PTH. It can be associated with vitamin D deficiency in the absence of failure, variable degrees of hormone sensitivity and specific phenotype renal. The basic abnormality resides in the gene encoding the cyclic AMP system < (GNAS). The initial description of pseudohypoparathyrodism was made by Fuller Albrigth in 1942.
Objective: To describe a case of pseudohypoparathyroidism.
Methods and results: We present du 11 years old girl with neurological growth retardation, 153 cm (p50) tall, thickening of joint condyle of knees, short a IV and V metacarpal bones, genu valgus and without calcifications of muscles or bones. She presented with seizures a serum calcium of 5,5 mg dl, PTH 446 pg/ ml magnesium 1,8 mg /dl phosphate serum 10,8 mg dl urinary phosphate 18,9 mg/ dl CT of brain showed basal ganglia calcifications, 25ohd2 < 4 and 25ohD3 >28. Bone densitiy -3,4 DE spine and -1,8 DE hip. No family history of bone disease. Study genetics Methylation of exones PasSXlas and exon A7B without methylation loss off the genes locus. Diagnostic Pseudohypoparatiroidism.
Conclusions: Patients with pseudohypoparathyroidism (PH)subtype 1b have an isolated resistance to PTH ,without a responsible molecular abnormality but a characteristic phenotype consisting of short stature, obesity, moon face, mental retardation, subcutaneous and basal ganglia calcifications, skeletal defects, shorts metacarpal bones and craneostenosis. Ours patient had this type, patients with (PH) type Ia have other hormonal alterations involving protein G. These showed be watched treatment of this disease is with calcium and vitamina D.

P3-d2-1248 Bone, Growth Plate and Mineral Metabolism 8

Risedronate in the ambulatory management of infant and child with osteogenesis imperfecta in a country with difficult access to pamidronate

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Background: OI it's a collagen disorder with recurrent skeletal fracture due to increase of fragility, after the Gloreiux report of eficay and safety in children Pamidronate is the bidphosphonate of choice in many countries. In our setting, the acce of many children it's difficult due to limitation of children for hospitalization and acces to this medication
Objective and hypotheses: Discuse the Densitometer and clinical evolution of one infant and one gilr with Clinical Diagnosis of OI.
Methods: DXA follow up it's presented and the tolerance and fracture sequence in this children, 0,2 mg/kg sem was started with previos treated vi-

tamn D deficiency and with calcium optiomazed diet. The rate of fractuire are describe in this children.
Results: The infant have rate of 8 to 1 fracture/year and increase con Bone Mineral content and densitometer, better aligneament and better motor development after Risendornate traeament. The girl Normalize her densitometer paramethers afther Risendronate actually it's in follow up of bone mineral accretion with general bone protective recomendations.
Conclusions: In case with OI when parenteral therapies are not disponiobles, Monitor of oral bisphosphonates it's un alternative if the parent's are agree and the fracture evolution don't have any posibility of treeatment.

P3-d1-1249 Endocrine Oncology 2

Incidence and risk factors for ovarian failure after haematopoietic stem cell transplantation

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Background: Hematopoietic stem cell transplantation (HSCT) frequently results in ovarian failure.
Objectives: To assess the incidence and risk factors for ovarian failure, and the need for hormonal induction of puberty after HSCT in childhood this study was performed.
Methods: In a retrospective single center cohort study, patients with the following criteria were eligible:
1. HSCT performed during childhood (< 18 years),
2. Survival at least 2 years after HSCT,
3. Age >10 years at start of study.
Data collected included: age at time of study and at HSCT, diagnosis for HSCT, conditioning regimen, date of last follow-up, date of menarche, Tanner stage, date of diagnosis of gonadal failure and hormonal induction of puberty/hormonal replacement therapy.
Results: Of 141 eligible girls 109 girls were followed up in our center and included in this study. The cumulative incidence of ovarian failure was 61.5%. Hormonal induction of pubertal development was needed in 33 of 102 girls (32%) who were (pre-)pubertal at HSCT.The cumulative incidence of ovarian failure was significantly (p=0.001) associated with pubertal stage at HSCT: 49% (35/71) in pre-pubertal girls, 81% (25/31) in pubertal girls and 100% (7/7) in post-pubertal girls.Cox regression analysis, accounting for follow-up time, showed that neither diagnosis (relative risk (RR) 1.6 for malignant versus benign hematological disease, p=0.16) nor conditioning with total body irradiation (TBI) (RR 0.9 for conditioning including TBI versus chemotherapy only, p=0.72) were significant risk factors for ovarian failure.However, in girls who received a conditioning regimen with chemotherapy only (n=51), the RR for ovarian failure with a regimen including Busulfan as compared to a regimen without Busulfan was 3.6 (p=0.03).
Conclusions: The cumulative incidence of ovarian failure after HSCT in childhood is high. Risk factors include a more advanced pubertal stage at HSCT and the use of Busulfan in the conditioning regimen.

P3-d1-1250 Endocrine Oncology 2

A rare case of Cushing syndrome by ectopic-ACTH

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Background: Cushing's syndrome (CS) is defined as the set of signs and symptoms caused by hypercortisolemia, CS by ectopic ACTH production is rare, particularly in the pediatric population, being usually associated with carcinoid tumors.
Objective and hypotheses: To report a case of CS caused by ectopic ACTH production.
Methods: A 16 year-old, white-male, with signs of CS who presented body weight increase of 10kg, acne and stretch. Laboratory results compatible with hypercortisolism (serum cortisol and ACTH elevated and urinary cortisol: 5005mcg/24h) were observed. His high-dose dexamethasone suppression test was responsive and an MRI of the pituitary gland demonstrated a 0.4 cm nodule in his adenohypophysis. A transphenoidal surgical resection was made at the pituitary microadenoma and the histopathological analysis of pituitary parenchyma revealed no abnormalities. His clinical condition worsened (refractory hypertension, diabetes mellitus, osteoporosis, pulmonary artery thromboembolism and emotional lability) and persistent laboratory results of hypercortisolism (maintenance of elevated ACTH and cortisol). Petrosal sinus catheterization was performed wich was consistent with CS caused by ectopic ACTH production. His chest CT demonstrated a 0.9 cm nodule in the mediastinal left paraaortic region.
Results: Surgical resection of the mediastinal nodule was performed and its histopathological analysis was suggestive of carcinoid tumor that involved a mediastinal lymph node. After surgery, he presented a weight loss and improvement in glycemic levels, blood pressure, mood, and back pain, associated with normalization of urinary cortisol (98 mcg/24h) and ACTH (33 pg/mL).
Conclusions: Ectopic ACTH production is a rare CS etiology, providing diagnostic challenges for clinicians. This report highlights the importance of an accurate diagnosis, so that patients may have an early and appropriate treatment, which would avoid the complications of CS.

P3-d1-1251 Endocrine Oncology 2

Endocrine complications and parameters of metabolic syndrome in survivors of childhood solid tumors

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Background: The improvement in survival of children with malignant tumors in recent decades has been achieved at the cost of serious late effects.
Objective: To evaluate adverse endocrine outcomes and components of the metabolic syndrome in survivors of malignant solid tumors of childhood and to identify their risk factors.
Methods: The medical records of 139 childhood survivors of non-brain solid tumors (group 1) attending the endocrine clinic of a pediatric tertiary medical center were reviewed for medical history, physical examination findings, and laboratory tests. Outcome measures were frequency and types of endocrine dysfunction and metabolic syndrome parameters. Findings were compared with a group of 140 childhood survivors of hematological malignancies (group 2).
Results: Mean duration of follow-up in both groups was 9.5±4.8 years (range 1.5-29.5 years). At least one endocrine abnormality was found in 44 patients in group 1 (31.7%) and in 33 in group 2 (23.6%). Endocrine abnormalities in group 1 included hypogonadism (11.5%), hypothyroidism (9.4%), short stature (9.4%), growth hormone deficiency (8.6%), and components of the meta-

bolic syndrome (9.4%), with no significant difference from group 2. Height-SDS was significantly lower in group 1 than in group 2 (p=0.039), with a tendency of a decrease during follow-up in both groups, but more significant in group 1 (p=0.007). BMI-SDS was significantly lower in group 1 than in group 2 (p=0.016), with a tendency to increase during follow-up in both, with no significant difference between them. On logistic regression analysis, treatment with cranial radiation, local radiation, and bone marrow transplantation was associated with a significantly higher hazard of endocrine complications.
Conclusions: The presence of late endocrine effects in a high percentage of childhood solid tumors survivors indicates a need to optimize screening for endocrine disorders in this population with institution of early intervention.

P3-d1-1252 Endocrine Oncology 2

Birth parameters and neoplasm diseases in children

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Background: Birth body weight (BW) can be one of determinants of postnatal cancer occurrence.
Objective and hypotheses: Assessment of connection between natal parameters and children's cancers occurrence and evaluation of children' s growing process from cancer diagnosis moment.
Methods: Study group: 140 children (80 boys) (1,29-21,33 yrs,average age 9±5,49 yrs) with cancers diagnosed:1995-2013. Birth parameters were analyzed as well as growing process from diagnosis moment on basis of body height (H) and weight (W) measurements . Children were divided into groups (gr.): ALL, ANLL, NHL, HD, solid tumors and 2 groups with age at diagnosis < 6 and >6yrs.
Results: In whole study group average BW and birth length were in normal range. Boys had bigger BW than girls (3604,09±613,25g vs.3236,53±447,79g,p=0,0003). There were 56.3% of boys in
ALL + ANLL group. ALL gr. differed from ANLL gr.(3627,71±595,62g vs.3146,25±495,81g,p=0,02 and 55,16±3,51cm vs. 50,57±3,64cm,p=0,006) and from control gr.(3336,97±515,74g,p=0,03).
In ALL gr. BW was lower in children diagnosed < age of 6 than >6 yrs (3572,07±507,6 vs. 3728,57±754,94g, p=0,61).
At conception mothers and fathers of children with ALL+ANLL were younger than the ones of children with NHL + HD (26,49±4,22 vs.24,11±5,37,p=0,009 and 29,16±4 vs.26,75±6,03,p=0,0019). Breast-feeding (in mths) in ALL gr. was longer than in ANLL gr.(7,04± 439 vs.2,6 ± 2,19, p=0,015).
At diagnosis: Height SDS: 0,62±1,86, Weight SDS: 0,5±1,91.W SDS decreased 6 mths after diagnosis (-0,23±2,14,p=0,03), after 6-18 mths it was:0,35 ± 2,03. H SDS decreased from diagnosis, after 6-18mths it was:0,004 ± 1,75 (p = 0,038) and> 18 mths: -0,69±2,14(p =0,008).
Conclusions:
1. Higher BW, especially in boys, may be one of determinants of postnatal cancer occurrence.
Further research and extension of study group is essential.
2. Children's process of growing needs monitoring during and after anti-cancer treatment.

P3-d1-1253 Endocrine Oncology 2

Evaluation of electrolyte serum levels and inflammatory parameters in children with newly diagnosed acute leukaemias (ALL, ANLL)

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Background: Electrolyte disturbances are common in children with diagnosis of acute leukemias (ALL, ANLL), especially during anti-cancer treatment.
Objective and hypotheses: Electrolyte disturbances are common in children with diagnosis of acute leukemias (ALL, ANLL), especially during anti-cancer treatment.
Methods: Study group: 47 children (28 boys) (37ALL, 10ANLL) (age at diagnosis:1-18yrs, average age:7,39±5,24yrs).
Results: Only 1 child with ANLL vomited before diagnosis, none had diarrhea and had taken drugs disturbing electrolyte balance.
Mean serum level of sodium (Na) in ALL group was significantly lower than in ANLL gr. (138,5±2,12 vs. 140,5±2,95mmol/l, p=0,04). Level of potassium (K) was lower in ANLL gr. than in ALL gr. (3,86±0,35 vs. 4,11±0,41mmol/l). At moment of diagnosis 5 children (10,64%)(2 ALL, 3 ANLL) had hypokalemia (K concentration< 3,5 mmol/l).
7 children with ALL had decreased inorganic phosphorus (P) concentration (conc.).
In all children average creatinine conc. as well as total calcium (Ca) conc. were within normal ranges. Relations between K and creatinine conc.(r = -0.27, p = 0.009), D-dimers were noticed (r = -0,36, p = 0,025) and between WBC and Na (r=-0,28, p=0,07), K (r=-0,32, p=0,02), P (r= -0,3, p=0,01). RBC correlated with Ca(r = 0,41, p=0).
Correlations between Ca and magnesium (Mg) level (r=0,47, p = 0), P (r=0,46, p=0,001), CRP (r= -0,43, p=0,001), fibrinogen (r = -0,27, p = 0,028), antithrombin III activity (r=0,32, p = 0,028) were observed. P correlated with LDH activity(r =-0,45, p=0,002) and CRP conc. (r= -0,34, p=0,038), and Mg with fibrinogen conc.(r=-0,29, p=0,019).
Conclusions:
1. All children with hypokalemia in ANLL group were diagnosed as acute monocytic leukemia.
2. It is advisable to monitor serum electrolyte levels in children with newly diagnosed neoplasm diseases. Children with ANLL need special supervision in this matter.
Further research and extension of study group is essential.

P3-d1-1254 Endocrine Oncology 2

Ectopic ACTH syndrome in a child, caused by yolk sac tumor

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Background: The ectopic ACTH syndrome at the child age is an extremely rare disease. In literature there are absent descriptions of cases of the ectopic ACTH secretion caused by of yolk sac tumor.
Objective and hypotheses: To describe case of the ectopic ACTH syndrome in a child, caused by tumor of the yolk sac tumor.
Methods: In a newborn boy, in the area of perineum, a tumor-like structure was determined, which at MRI was visualized as a coccygeal tumor expanding into pelvis and the left gluteal area, measuring 50×52×73 mm. The alpha-fetoprotein (AFP) level exceeded 300 mIU/ml. At the month age the tumor was extirpated. Histological study revealed the yolk sac tumor.
Results: From 6 months, delay of growth began to be observed (height SDS at 6 months - 1.34, at 1.5 year - 3.9), progressing increase of body mass index (at 6 months - 16.8 kg/m^2, at 1.5 years - 29.1 kg/m^2), classic cushingoid features. At 8.00, ACTH 40.6 pg/ml, cortisol 609 nmol/l, at 21.00, ACTH 46.6 pg/ml, cortisol 697 nmol/l. At performance of high-dose dexamethason suppression test, ACTH 46.8 pg/ml, cortisol 972 nmol/l, which allowed suggesting the ectopic ACTH syndrome? In the University clinic Hadassa (Jerusalem, Israel), PET with administration of Gallium68-DOTA-NOC was performed. There was revealed a formation from soft tissue between gluteal muscles from both sides, spreading along pelvis. The determination of ACTH and cortisol levels in venous blood from various areas of the whole body showed the source of ACTH hypersecretion to be located in the right posterior sacral-coccygeal area. Removal of the tumor was performed. At histological study, the yolk sac tumor was verified. After removal of the tumor, in the child, symptoms of hypercorticism were regressed, the height velocity increased, the body mass index was normalized.
Conclusions: In the child with the yolk sac tumor, after surgical treatment and chemotherapy, there was developed relapse of tumor accompanied by ectopic ACTH secretion.

P3-d1-1255 Endocrine Oncology 2

Pediatric craniopharyngiomas

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Background: Craniopharyngiomas are epithelial tumors of the sellar and suprasellar region derived from Rathke cleft, they are among the most common forms of sellar tumors in children. Although they are histologically benign they may have severe complications and they often recur.
Objective and hypotheses: The aim of our study was to analyze the clinical, radiological and therapeutic options in pediatric craniopharyngiomas.
Methods: The medical records of 47 patients (28M/19F) harboring a craniopharyngioma were reviewed.
Results: Mean age at diagnosis was 11.2 ± 5.4 years. Appealing symptoms were neuro-ophtalmological signs in 73% with intracranial hypertension in 27%, endocrine disorders like growth or pubertal retardation, polyuria polydipsia, signs of pituitary deficiency or hypothalamic dysfunction bring the patients to consult in 27%. On the biological level, partial or panhypopituitarism was found in 72% and diabetes insipidus was noted in 46.8%. Visual impairment was found in 72% with blindness of one or both eyes in 27%. Mean size of the tumor was 37 ± 10.7 mm. All patients were operated on sometimes more than once; radiotherapy was used in 20.5%.
Conclusions: Craniopharyngioma is a rare tumor which may have severe endocrine, neurological and visual repercussions; it often needs iterative surgery sometimes combined with radiotherapy.

P3-d1-1256 Endocrine Oncology 2

The first report of cabergoline-induced immune hemolytic anemia in an adolescent with prolactinoma

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Background: Prolactinomas are common pituitary tumors which cause of gonadal dysfunction and infertility related to hyperprolactinemia. Dopamine agonists are the first line treatment in these patients cause of highly effective. Cabergoline leads to significant reduction in serum prolactin levels and tumor size in patients with prolactinoma. Additionally, cabergoline is more effective and better tolerated than bromocriptine. Treatment with transsphenoidal pituitary surgery or radiotherapy should be chosen for patients with intolerance or resistance to these agents. Dopamine agonists have been associated with adverse effects as nausea, vomiting, psychosis. We report here a more rare case with cabergoline induced immune hemolytic anemia. She has cabergoline treatment history for prolactinoma and presented with weakness, fatigue, nausea, and paleness. Laboratory findings revealed severe anemia related immune hemolysis. There were no causes identified to explain hemolytic anemia except cabergoline. Therefore, cabergoline therapy was stopped and subsequently hemolytic anemia did not developed again.
Conclusions: In conclusion, this is the first adolescent case with prolactinoma who has cabergoline induced hemolytic anemia. We often should be careful for rare side effects as hemolytic anemia. Thus, patients should be consecutive checks for complete blood count values at regular intervals.

P3-d1-1257 Endocrine Oncology 2

Low level of vitamin D in children with newly diagnosed neoplasm diseases?

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Background: In recent years an increasing number of studies have suggested that a low level of vitamin D contributes to development of many sorts of chronic diseases. In respect to many malignancies, vitamin D insufficiency is only one out of many risk factors. Recent studies concerned only adults.
Objective and hypotheses: Evaluation of serum vit.D((25-OH)D) concentration and phospho-calcic parameters in children with newly diagnosed neoplasm diseases before anti-cancer treatment initiation.
Methods: Study group: 17 children (10♂), 0,67-17,5 yrs, average age: 8,83±5,65 yrs. At diagnosis moment none of the children was receiving vit.D. In 8 children leukemias were diagnosed (6 ALL, 1 ANLL, 1 CML), in 3-lymphomas(1 NHL, 2 HD) and in 6-solid tumors.
Results: In whole study group average serum concentration of vit.25(OH) D was decreased: 21,59±9,39ng/ml (9,8-36,8), like inorganic phosphorus: 4,39±0,54mg/dl (3,53-5,47). Average alkaline phosphatase concentration was within normal range: 150,13±60,34U/l(67-269), like total calcium 9,59±0,38mg/dl (8,88-10,19) and parathyroid hormone concentration: 27,81±16,6pg/ml(3,09-55,9)
6 children (35,3%) had extremely low vit.D concentration and in 3 children it was within normal range. In children with ALL leukemia and lymphomas average vit.D concentration confirmed significant vit.D deficiency(19,54±9,66 and 15,23±6,98ng/ml). A trend between vit.D concentration and children's age was observed.
4 children had decreased level of parathyroid hormone and 10 children (58,8%) - inorganic phoshorus concentration. None of the children had hypocalcemia.
Conclusions:
1. Decreased vit.D concentration occurs in children with newly diagnosed neoplasm diseases, especially in patients with leukemia and lymphoma. Further research and extension of study group is essential.
2. It is advisable to monitor vit.D concentration in children with newly diagnosed cancers.

P3-d1-1258 Fat Metabolism, Obesity 13

Metabolic differences between prepubertal and pubertal obese children

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Background: Obesity becomes a global problem worldwide. Many studies report on factors conferring co-morbidities such as hyperinsulinemia, leptin and adiponectin levels. Several studies analyze differences between young obese children and adolescents with conflicting results.
Objective: To analyze and compare values of insulin, leptin and adiponectin in two cohorts: prepubertal children (2-9 years), and pubertal children (10-16 years).
Methods and results: Group A (prepubertal children) consisted of 59 individuals (30 boys). Group B (pubertal children) consisted of 139 individuals (75 boys). Thirty healthy children were analyzed for leptin and adiponectin as a control. Self reported family risk factors were recorded using questionnaire. Insulinemia and glycemia were measured during a standard OGTT. HOMA index was calculated according to a standard formula. Leptin and adiponectin levels were measured with ELISA method.
Results: BMI was 27.7±4.6 kg/m^2 in the group A, and 32.4±4.9 kg/m^2 in the group B. One or more risk factors were recorded in 47.3% of obese children. Peak insulinemia was significantly higher in the group B, 99.5 μU/ml average (range 6.3-300 μU/ml) vs 64.3 μU/ml in the group A (range 3.3-300 μU/ml) ($p< 0.05$). No gender differences were found. Average leptin level was 28.2 ng/ml in the group A and 32.4 ng/ml in the group B with no significant dif-

ference, but significantly higher compared to the control group. Average level of adiponectin was significantly lower in the older group (12.8 µg/ml vs 21.2 µg/ml) reaching statistical difference (p=0.05). HOMA index was also higher in the group B (p< 0.05).
Conclusion: Insulin resistance increases with the age in obese children. Although leptin levels were similar in both groups, low adiponectin levels indicated much higher risk for insulin resistance and cardiovascular complications in older children with obesity. Therefore, therapeutic intervention in obese children should begin at a younger age.

P3-d1-1259 Fat Metabolism, Obesity 13

How early is dyslipidaemia among obese children in the age group of 6 to 18 years among North Indian population?

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Background: Childhood obesity is associated with dyslipidemia and increased risk of metabolic syndrome.
Objective and hypotheses: To assess dyslipidemia among obese children (Body Mass Index-BMI > 95th centile) aged 6-18 years.
Methods: Eighty 6-18 years-40 obese and 40 age and sex matched non-obese controls were recruited. Height, weight, BMI and blood pressure (BP) were recorded. Fasting and post-prandial blood sugar and lipid profile (Spectrophotometry) were measured.
Results: Mean age was similar in both cases and controls 9.42±2.41 years. BMI was significantly higher in obese vs controls 27.9±2.84kg/m^2 ,16.01±1.22 p < 0.001. Mean BP and fasting and post-prandial sugar profile were comparable in both groups, p>0.05. Serum Cholesterol in obese vs controls was 145.5±18.04mg/dl, 139.65±16.74mg/dl, p=0.13. Serum Triglyceride (TG) raised in obese children (134±42.88 mg/dl) vs controls (91.37±16.22) p< 0.001. Mean High Density Lipoprotein (HDL) low in cases than controls (48.32±7.93mg/dl, 54.25±9.41, p< 0.001). Serum Low Density Lipoprotein not significant. 27/40 (67%) were prepubertal age< 10 years and 13/40 (33%) pubertal age>10 years. Among obese pre-pubertal, 15% had dyslipidemia - both TG and HDL were significantly affected p< 0.001. 60.5% of post pubertal obese had deranged lipid parameters cholesterol (157.31±41.1,vs135.92±15.08mg/dl; p=0.005), TG(157.31±47.16vs80.92±15.08mg/dl; p< 0.001), HDL (45.23±8.97vs53.76±8.78mg/dl;p=0.02)andLDL(88.15±30vs79.38±8.51mg/dl; p>0.05). Only 3 had Acanthosis nigricans, 1 had hypertension.
Conclusions: Thus,15% of pre-pubertal and 60% pubertal children had dyslipidemia indicating increased risk for premature atherosclerosis and metabolic syndrome.Blood sugars and BP not affected. Therefore puberty adversely affected the metabolic control hence healthy lifestyle should be emphasized in adolescence to prevent long term complications.

P3-d1-1260 Fat Metabolism, Obesity 13

Is early age at adiposity rebound a risk factor of obesity in pubertal stage?

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Background: Childhood overweight (OW) and obesity (O) has become an epidemic in the developed countries. It is important to identify early determinants of development of these conditions.
Objectives and hypotheses: To determine early factors-candidates of O development in puberty.
Methods: Randomized retrospective study of 252 children (122 girls, 130 boys; aged more than 12 years) were conducted in the 8th State Paediatric Outpatient Clinic(Minsk) in 2012-2013 yrs. Gestational age(GA); feeding until 4 months (breast, bottle, mixed); anthropometric data (weight, height, BMI) at birth, 4-12 months, 1,5, 2-6, 12 years were estimated. Patients were divided into groups according to their BMI in 12 years: G1 normal-weight (n=92), G2 OW (n=20), G3 O girls (n=10); B1 normal-weight (n=88), B2 OW (n=17), B3 O boys (n=25). Results were processed using SPSS17.
Results: There were no difference of GA in girls (G1-G3 p=0,9; G1-G2 p=0,1; G2-G3 p=0,5). The decreasing of GA were noticed in O and OW boys: B3 38,7±2,5, B1 39,5±1,16 (p=0,03); B2 38,7±1,6 (p=0,01). The reliable differences in the types of feeding and development of OW and O in 12 years weren't noted (G1-G3 p=0,2; G1-G2 p=0,6; G2-G3 p=0,2; B1-B3 p=0,7; B1-B2 p=0,4; B2-B3 p=0,1).
There were the increasing BMI G3 in comparison with G1 in 4 (p=0,01), 5 (p=0,005), 6 years (p=0,005). BMI G2 were higher than G1 4 (p=0,001), 5 (p=0,001), 6 years (p=0,004). The age of adiposity rebound was 2 G3 (p=0,05), G2 3 years (p=0,1).
BMI B3 were higher than B1 6-8, 10-12 months (p(6m)=0,0001; p(7m)=0,01; p(8m)=0,003; p(10m)=0,01; p(11m)=0,01; p(12m)=0,02); 2-6 years (p(2y)=0,006; p(3y)=0,04; p(4y)=0,0001; p(5y)=0,03; p(6y)=0,001). There were no reliable differences in B2. Adiposity rebound in O boys was 2 (p=0,001), OW 4 years (p=0,48).
Conclusions: Overweight and obesity in pubertal age are characterized by early age at adiposity rebound in boys (4 years(p=0,48), 2 years(p=0,001) and girls (3 years(p=0,1), 2 years(p=0,05).

P3-d1-1261 Fat Metabolism, Obesity 13

Vitamin D deficiency and metabolic syndrome in obese children

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Background: Vitamin D deficiency may increase the risk for metabolic syndrome.
Objective and hypotheses: The study assessed the relationship of serum 25-Hydroxyvitamin D (25OHD) and metabolic syndrome in obese children.
Methods: Age, pubertal stage, body mass index (BMI-SD), body fat index, waist circumference, 25OHD levels, PTH, fasting glucose, insulin resistance (IR) index calculated by HOMA-IR were evaluated in 57 obese aged between 7-17 years. All patients was derived for two groups (BMI< 3SD and BMI >3SD).
Results: Median serum 25OHD level was 16,6 ng/ml. Vitamin D deficiency (25OHD< 20ng/ml) was found in 40 (70%) and insufficiency (25OHD 21-29 ng/ml) in 13 (23%) obese children. There were no significant differences in the vitamin D deficiency in groups with BMI< 3SD/ BMI >3SD, and abdominal / non abdominal obesity**.** Impaired glucose tolerance was diagnosed in 8 and diabetes type 2 in 2 patients with vitamin D deficiency. 25OHD levels were negatively associated with BMI (r= -0,41, p< 0,05), FMI (r= - 0,53, p< 0,05), PTH (r = -0,34, p< 0,05), icreasing in BMI>3SD group. Frequency of IR significantly increased in vitamin D deficiency group (p< 0,05).
Conclusions: Low 25OHD levels have a high prevalence in obese children and adolescents. Combination of vitamin D deficiency (25OHD< 20 ng/ml) and obesity with SD BMI >3 may be an important predictor of metabolic syndrome in this population.

P3-d1-1262 Fat Metabolism, Obesity 13

Type 2 diabetes and impaired glucose tolerance due to severe hyperinsulinism in patients with 1p36 deletion syndrome and Prader-Willi like phenotype

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Background: Deletion of the subtelomeric region of 1p36 is one of the most common Prevalence of this deletion is estimated to be 1 in 10,000 to as high as in 1 in 5,000, with a 2:1 female to male ratio, making it the most common terminal deletion.
Objective and hypothesis: In 1p36 monosomy the presence of obesity is poorly described and/or glucose metabolism disorders is very rarely reported. Hovewer, the presence of a typical Prader-Willi-like (PWS-like) phenotype in patients with 1p36 monosomy is very debated.
Population and/or methods: We describe two patients, 6 years 2 months and

10 years 1 month old females, referred to our Hospital for severe obesity and PWS-like phenotype. These patients showed important obesity (BMI 26,4 and 27,7 respectively) with hyperfagia, and developmental delay.
Results: Basal hormonal investigation showed normal thyroid function, adrenal function, but very important hyperinsulinism (insulin 54.5 and 49.2 mU/ml, respectively). In patient 1 glycaemia was 75 mg/dl (HOMA-R 10.09) and HbA1c 6.1%, whereas in patient 2 glycaemia was 122 mg/dl (HOMA-R 14.82), and HbA1c was 6.6%. The oral glucose tolerance test showed in the patient 1 an impaired glucose tolerance with marked insulin resistance (respectively, peak insulin level 197 and 279 μU/mL).
Conclusions: Some patients with 1p36 monosomy show PWS-like physical and laboratory characteristics such as obesity with hyperinsulinism and impaired glucose metabolism causing tipe II diabetes mellitus. Further studies are necessary to evaluate this aspect.

P3-d1-1263 Fat Metabolism, Obesity 13

Partial lipodystrophy in a 12-year-old African-American male

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Introduction: Partial lipodystrophy is a genetic disorder characterized by defects in adipose tissue accumulation, with subcutaneous abdominal fat, femorogluteal fat and appendicular skeleton being the most affected areas. The common findings associated with congenital disorder are insulin dependent diabetes with severe insulin resistance, soft tissue hypertrophy and dyslipidemia.
Case study: We report a 12 year old African-American male with history of poorly controlled T1DM for three years. Physical exam was remarkable for severe acanthosis nigricans with skin tags over neck and axilla, soft tissue hypertrophy of nose and lips, minimal subcutaneous abdominal fat. Review of systems was negative except for occasional headaches, progressive episodes of fatigue and decline in school performance. At initial presentation, HbA1c was 12.3%, islet cell AB, GAD AB and IA2 AB were negative, C-peptide was elevated to 7.06 ng/ml (range 0.8-3.1), there was mild dyslipidemia and low-normal levels of leptin 0.5 and 1.8 ng/ml (range 1.4 - 16.5). Initial treatment to maintain euglycemia required daily insulin of 3 U/Kg/Day. U500 insulin was started with mild improvement in HbA1c but dyslipidemia worsened (HDL 36 mg/dl and TG 238 mg/dl) and ALT and AST were elevated (34 and 36 U/L). His thyroid and adrenal function were normal. Testosterone level was 270 mg/dl, revealing early puberty. We suspected partial lipodystrophy based on clinical and biochemical findings.
MRI of whole body done to quantify fat distribution revealed generalized muscle hypertrophy with relative paucity of subcutaneous and intra-abdominal fat, in association with periarticular and intramedullary high signal lesions within the appendicular skeleton. MRI of the brain was normal. Leptin treatment and CIDEC mutation analysis are pending.
Conclusions: Lipodystrophy evaluation is warranted in cases of insulin resistance diabetes in children.

P3-d1-1264 Fat Metabolism, Obesity 13

A review of childhood obesity seen at a tertiary Children's Hospital

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Introduction: The incidence of childhood obesity in the United Kingdom has tripled over 25 years and data from the 2011 national health survey in England showed 30.3% of children aged 2-15 years old are either overweight or obese[1].
Methods: Obese children presenting between 2006-2012 were audited. Children with recognised syndromes, diabetes, underlying endocrine and oncology diagnoses were excluded. Insulin resistance(IR) was diagnosed by a Homeostatic model assessment (HOMA-IR) index >99th centile for age and sex[2], impaired glucose tolerance (IGT) if 2-hour blood glucose (BG) >7.1mmol/L[2], type 2 diabetes (T2DM) when fasting BG ≥7.0mmol/L, 2-hour BG ≥11.1mmol/L [3] or glycated haemoglobin (HbA1C) ≥.6.5%(48mol/mmol)[4], dyslipidemia if total cholesterol (TC) >5.2mmol/L, triglyceride (TG) >1.7mmol/L, HDL< 1.03mmol/L[5]. Non-alcoholic fatty liver disease (NAFLD) was diagnosed following routine ultrasound.
Results: Eighty-five children (48% boys) were eligible for the audit. Median age 13.2 (0.68-16.5) years old. Mean BMI 32.8kg/m^2 (mean SDS +3.19). Fifty-four had IR, 1 was diagnosed with T2DM, 12 had NAFLD, 31 had dyslipidemia and 13 were concomitantly diagnosed with PCOS. Six had normal investigations and 11 had incomplete investigations. Forty percent (n=34) were started on or offered Metformin, however this was not recommended in 14/85 despite evidence of IR and/or PCOS. Follow-up data (3-23 months) was available for 34 patients. At 6 months follow-up (n=27), 14 gained weight. Of the 33 discharges, 6 were discharged despite increasing weight, and 13 with at least 1 associated co-morbidity.
Conclusion: Childhood obesity is associated with higher cardiovascular risk and metabolic syndrome. Our audit illustrates the difficulties associated with managing these patients. Management requires a standard guideline advocating appropriate assessment, risk stratification and intervention in clinical management.

P3-d1-1265 Fat Metabolism, Obesity 13

The role of spontaneous physical activity on obese children's health

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Background: Children obesity is a growing disorder leading to a reduced quality of life during childhood and adolescence and to an increase of metabolic-related diseases. Primary intervention requires improving our knowledge about its causes.
Objective and hypotheses: The aim of the study was to observe the relationship of spontaneous physical activity and aerobic fitness with some indicators of health in obese children.
Methods: Forty-four overweight-obese (9.60±1.53 ysr) were recruited by the Regional Centre of Auxology and Pediatric Nutrition at the "S. Liberatore" Hospital (Atri-Italy). Body composition, blood pressure, plasma value of glucose and insulin were investigated. Insulin resistance was measured through the homeostatic model assessment for insulin resistance (HOMA-IR). Spontaneous physical activity of participants was measured through a multisensor devide (i.e. Sensewear Armband) for 7 consecutive days, and 6-min walking test (6MWT) was used to estimate aerobic fitness.
Results: Linear regression model showed that daily sedentary time (B=-0.406; p:0.001) and very vigorous-intensity physical activities (VVIPAT) (B=0.649; p:0.04) were independently correlated with nocturnal sleeping. The same was found for sleeping efficacy (i.e. nocturnal sleeping to nocturnal lying down). When BMI was inserted in the analysis as predictor, results did not change and its effect was not found significant. Linear regression analysis also showed that 6MWT (B=-0.01; p=0.02), sedentary time (B=-5.191; p=0.002) and VVIPAT (B=-0.025; p=0.05) were independently correlated with BMI. HOMA-IR has been shown inversely correlated with VVIPAT (r=-0.326; p=0.01).
Conclusions: Our preliminary data suggest the importance of reducing children's sedentary time and increasing VVIPAT because of their direct and indirect (i.e. sleep-mediated effects) relationships with BMI and insulin resistance.

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Using cutaneous signs as clinical markers for metabolic complications in a group of overweight and obese children

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Background: Several studies had suggested an association between the presence of acanthosis nigricans, purple striae and metabolic complications of obesity (insulin resistance, alterations of carbohydrate metabolism and subclinical hypercortisolism).
Objective and hypotheses: To establish a clinical screening protocol for early detection of metabolic complications in overweight and obese children.
Methods: The study included 139 children (70 girls and 69 boys) evaluated for primary obesity between 2010 and 2013. The first evaluation included: anthropometric indexes (weight, height, BMI, waist circumference), cutaneous signs (acanthosis nigricans, purple striae), biochemical tests (morning cortisol, fasting glucose level, OGTT, basal insulinemia) and HOMA - IR was calculated.
Results: Dermatological signs were identified in 58.99% of all children (35.97% had purple striae, 7.91% were with acanthosis nigricans and 15.10% had both). Biochemical tests performed shown that 55.55 % of these patients had no alteration of carbohydrate metabolism or hypercotisolism. We determined that 84.21% of the children with no skin signs had normal biochemical tests. The rest of this study group (3 boys and 6 girls - 15.79%), had subclinical hipercortisolism, impaired glucose tolerance and hyperinsulinism. The 9 children were prepubertal or at puberty so other hormonal and metabolic factors may contribute to these alterations.
Conclusions: Recognizing and active screening of these skin changes in obese children is important for early identification of metabolic complications. It is a simple and cost effective method that can be applied by every healthcare professionals.

P3-d1-1267 Fat Metabolism, Obesity 13

Body composition and links with cardiovascular risk factors in childhood obesity

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Objective: Anthropometric assessment by means of bioimpedance analysis enables body composition to be determined, distinguishing between fat, lean and water compartments. This study sought to examine links between the different body compartments and a number of cardiovascular risk factors in a paediatric population.
Methods: In this cross-sectional study, 97 children (48 boys+49 girls) aged 7 to 14 were divided into two groups by BMI: obese group ([24+26]=50, BMI>p 97) and normal-weight group ([24+23]=47, BMI normal). Clinical variables (age, sex, weight, height, BMI and abdominal girth), and biochemical variables (total cholesterol HDLc and LDLc, triglycerides, glucose, insulin, HOMA-I) were examined, and bioimpedance analysis was performed (fat mass, lean mass and body water). Links were sought between variables for both groups, using linear correlation tests. Student's t test was used to test for intergroup differences.
Results: The body water compartment was greater in the normal-weight group than in the obese group ($p < 0.000$). A direct correlation was observed between abdominal girth and the body fat compartment both for the study as a whole ($p < 0.000$) and in the obese group ($p < 0.001$). Abdominal girth was greater in boys than in girls for the study as a whole ($p < 0.022$), but not when each group was compared separately. The lean mass compartment was greater in boys than in girls, both for the study as a whole ($p < 0.028$) and for the normal-weight group ($p < 0.009$). A larger fat mass compartment was associated with higher triglyceride levels and lower HDLc levels, both for the study as a whole and for the normal-weight group.
Conclusions: Childhood obesity is marked by a decrease in the percentage of body water and an increase in the fat and lean mass compartments (with no clear predominance of one over the other). Abdominal girth increases at the expense of fatty tissue. Greater fat mass is associated with elevated serum triglyceride levels and a decrease in HDLc.

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Lifestyle programme for healthy living in childhood

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Background: Paediatricians deal with an increasing number of obese children. Obesity affects all socio-economic groups, both sexes and all age groups in increasing numbers. Many factors have been implicated: increasing affluence, increasing portion size, increased saturated fat in convenience foods, a sedentary lifestyle, more television watching, less exercise and an increasing amount of stress in the modern world. Unfortunately, medical practitioners do not have a good success rate in inducing weight loss in obese patients.
Objective: Keeping in mind the relatively poor success rate of dietary interventions in inducing weight loss in children, the objective was to design a healthy lifestyle programme which is likely to be sustainable.
Method to develop the programme: Considering the evidence of increased ingestion of fruit juices in the past 25 years, the influence of increasing screen time (cellular phones, televisions and computer games) and the effect of having fewer friends on the amount of exercise in childhood, a programme which addresses these factors was developed.
Structure of the programme: This is a 12-step programme; one step is implemented every week for a three-month period. It is essential that the whole family be involved. The first step is to eliminate fruit juice and cola drinks; a 200 ml serving contains the equivalent of four heaped teaspoons of sugar. Secondly, a dog or a bicycle ought to be acquired, for natural exercise. Thirdly the child is encouraged to make a new friend, as it has been shown that the more friends a child has, the more time is spent in play. The complete programme will be discussed.
Implementation of the programme: The programme is slated for implementation from July 2013, for all children with obesity; children in the paediatric endocrinology clinic will be invited to participate, on the premise that a healthy lifestyle is for everyone.

P3-d1-1269 Fat Metabolism, Obesity 13

Medical and psychosocial implications of adolescent extreme obesity - acceptance and effects of structured care study (YES) - a consortium of the BMBF competence network obesity

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Background: Extremely obese adolescents are at risk for early mortality, somatic and psychiatric comorbidities, however they rarely seek medical care. The underlying reasons are poorly understood but patient inherent factors and the lack of treatment options may play a role.
Objective and hypotheses: To evaluate the acceptance and effectivity of a structured diagnostic and therapeutic program we aim to recruit adolescents from medical and non-medical settings.
Population and methods: In a multicenter study involving 5 university centers, we aim to recruit 1200 adolescents age 14-21 years, 50% extremely obese (BMI ≥35kg/m^2), 50% obese (BMI 30-34,9kg/m^2) over 24 months. The study comprises 4 subprojects (SP):
SP1 offers a detailed examination for somatic and psychiatric comorbidities. In a 9 year observational follow-up they receive individualized medical care. The acceptance of the program and the prevalence of comorbidities will be defined, and predictors will be identified.
SP2 is a RCT comparing a new psychosocial group intervention to improve self-esteem with standard care (dietary/exercise group counseling). Endpoints are compliance, health related quality of life and psychosocial aspects assessed by validated questionnaires.
In SP3 patients who undergo bariatric surgery will be enrolled in a structured preparation and follow-up program. Surgical outcomes will be assessed in comparison to a matched control group.
In SP4 we will perform an economic analysis of the financial burden associated with extreme obesity and a cost-effectiveness analysis of bariatric surgery.
Results: 110 patients have been enrolled in a pilot phase as of February 15, 2013 (recruitment started in July 2012).
Conclusion: This study will yield information on the somatic and psychosocial sequelae of adolescent extreme obesity and on the acceptance and efficacy of a structured medical care. The long-term goal is to improve medical and psychosocial structures for this patient group.

P3-d1-1270 Fat Metabolism, Obesity 13

Profile of circulating cytokines (IL-1α, IL-β, IL-2, IL-6, TNF-α, IFN-γ) in disturbances of body weight in children: anorexia nervosa (AN) vs. obesity (OB)

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Background: Expression of IL-2, IL-6, TNF-α is found in adipocytes, and IL-1 in fat tissue stroma. There is no reports comparing the circulating cytokines concentrations in a group of subjects with wide range of body weight - from undernutrition to obesity.
Objective and hypotheses: The aim of the study is the assessment of IL-1*α*, IL-1β, IL-2, IL-6, TNF-α, IFN-γ blood concentrations in girls with disturbed body weight.
Methods: In 80 girls: 30 with restrictive AN, 30 with OB and 20 healthy (H) serum IL-1α, IL-1β, IL-2, IL-6, TNF-α, INF-γ and insulin (INS) concentrations were established.
Results: Mean serum IL-1α (13.1±3.8 pg/ml) and IL-1β (2.6±0.9 pg/ml) in AN was significantly higher than in OB (4.7±1.4 pg/ml and 1.3±0.6 pg/ml respectively; $p< 0.05$) and H (6.8±1.5 pg/ml and 1.1±0.6 pg/ml, respectively; $p< 0.05$). Serum IL-2 in AN was significantly lower in AN compared to the other groups ($p< 0.05$). Mean serum IL-6 concentration was similar in AN (2.3±0.8 pg/ml) and H (1.9±0.5 pg/ml), but significantly lower than in OB (12.7±9.3 pg/ml) ($p< 0.05$). Mean serum TNF-α and IFN-γ were significantly lower in AN (0.7±0.1 pg/ml and 1.3±0.6 pg/ml, respectively) than in OB (1.7± 0.6 pg/ml; $p< 0.05$ and 6.1±2.5 pg/ml; $p< 0.001$), but similar as in H (0.9±0.7 pg/ml and 1.5±0.6 pg/ml; respectively). The significant positive correlation between serum IL-2, IL-6, TNF-α or IFN-γ and the negative relation between IL-1*α* or IL-1*β* and BMI or Cole's index in all examined subjects was noted ($p< 0.05$). There is also positive relationship between IL-2, IL-6 or IFN-γ and INS and negative one between serum IL-1α and IL-1β in all examined girls ($p< 0.05$).
Conclusions:
1. Decreased levels of IL-2, IL-6, TNF-α or IFN-γ in AN patients results only from low adipose tissue mass.
2. Our observations suggest the role of some of examined cytokines in insulin resistance mechanisms related to body weight.

P3-d2-1271 Fat Metabolism, Obesity 14

An example of a nutritional assessment tool

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Background: Childhood obesity is an important public health issue and bad eating habits are usually the cause for it. Nutritional assessment tools are available world-wide, but there's none yet developed for our country. Diet recommendations are an important part of the treatment of children with obesity, although the most difficult one to develop.
Objective and hypotheses: The objective of the study was to analyze a web-based nutritional assessment tool.
Type of study - cross-sectional. Sample - 40 obese children examined in the pediatric unit of the Mures Emergency County Hospital in the past year. Methods - general information (age, sex, environment), anthropometric measurements (weight, height, waist circumference), food frequency questionnaire (FFQ) adapted to regional foods, with 126 items.
Results: Of the 40 children initially included, only 22 have completed the entire FFQ and have their personal food pyramid constructed. The sex ratio favors the girls (68.18%), and 68.18% of them came from urban areas. None of the children had a normal food pyramid, in regard to the recommended number of servings, most of them consuming twice and three times the recommended number of servings. 77.22% of them consume the recommended dose of fruits and vegetables. 95.45% consume high amounts of fats

and 86.36% consume high amounts of foods rich in sugar and saturated fat.
Conclusions: This nutritional assessment tool is useful for identifying the food groups responsible for fat gain. It also gives recommendations for diet. It has the disadvantage of being time consuming, with poor compliance, only 55% of children having completed the test.
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P3-d2-1272 Fat Metabolism, Obesity 14

Fast-food consumption frequency and the influence on children's nutritional profile

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Background: Obesity is a nutritional problem that grows every day in Brazil, changing the nutritional status of children. This worrying fact is mainly attributed to poor eating habits and sedentary lifestyle.
Objective and hypotheses: This study aimed to evaluate frequency the fast-food of consumption in children and the influence in the nutritional profile.
Methods: Evaluated children 5-10 years old of both sexes, enrolled in a private school and public school. Anthropometric measurements were used as the measurement of weight and height for the realization of Body Mass Index (BMI), and classified according to World Health Organization (WHO), 2007. For the evaluation of food frequency was used a hedonic scale questionnaire with five faces of facial expression., containing foods common in childhood and corresponding: "Never Eats", "Eats little", "Eating More or Less", "Eating Sometimes" and "Always Eats".
Results: In the private school, 25% of sample were classified as obesity and 24% in overweight. Totaling 49% of sample were above the recommended standards. In public school, 51% of children were above the recommended standards; being 21% as obesity and 30% overweight. Correlating the fast-food and the nutritional status, it was found that children classified as obesity, had a higher frequency of fast-food.
Conclusions: Following trends of children nutritional profile in of children today, where traditional meals are replaced with snacks, with high consumption of foods like fast food and without physical activity, one should have special attention to the formation of healthy eating habits in childhood, benefiting their growth and development, and enabling a healthier adult life.

P3-d2-1273 Fat Metabolism, Obesity 14

School results, self esteem and quality of life in overweight children aged 11

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Background: Among psychosocial complications of pediatric overweight, low self-esteem (SE), stigmatization and impairment of quality of life (QOL) can lead to poor school performance. However, published studies show conflicting results that might be due to the complex psychological, social and biological determinants of obesity with many confounding factors.
Objective and hypotheses: To study the link between overweight and academic performance, SE and QOL in a population of children followed within a network for prevention and treatment of childhood obesity (RePPOP) in a French region.
Methods: 59 overweight children (49% obese, mean BMI 24.7) followed within the RePPOP, were included because aged 11. Their educational level was assessed through a national survey. SE was evaluated using the Rosenberg scale and QOL was measured using the Pediatric Quality of Life Inventory (PedsQL 4.0). Data on lifestyle and medical history of the child and parents were recorded through a questionnaire. 44 children (75%) were evaluable.
Results: Overweight children had school results similar to other children or even superior in mathematics: 79.1% had a sufficient level vs 73% in the general population. In french they reached 74.4% vs 77%. Their school year repetition rate was below the national one (6.7% vs 14%).
Quality of life and self-esteem of children in our sample did not seem affected: the global QL score was 78.73, equivalent to the QL measured in children without pathology. The global SE was estimated at 32.42/40.
Conclusions: The assessment of academic achievement, self-esteem and quality of life of a small sample of 44 overweight children who benefit from a global care program showed no alterations unlike what has been published. We can hypothesize that the care program could positively affect some of these parameters and / or that children with markedly impaired quality of life did not have access to this program. A larger study is needed to investigate this question.

P3-d2-1274 Fat Metabolism, Obesity 14

Gestational diabetes and obesity

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Background: Gestational diabetes (GD) is associated not only with increased risk of high birth weight (BW) in infants, but also with a long-term overweight and obesity.
Objective and hypotheses: To assess the influence of GD in both BW and obesity in children and adolescents.
Methods: We studied 1338 children and adolescents from 1 to 18 years of age, attended in Pediatric Nutrition and Endocrinology consultations at three tertiary hospitals. GD and BW were obtained by questionnaire. Sample was stratified by body mass index (BMI), according to Cole's international standard. We used SPSSv. 15 for statistical analysis.
Results: 45.7% of the subjects were obese, 25.4% overweight and 28.9% normal weight. The mean BW in the offspring of women with GD was 3492±654.12 g, significantly higher than in children of non-GD women (3311.16± 541.55 g); p= 0.05. Obese children had a significantly higher BW (3991g) compared to overweight (3269.3 g) and normal weight children (3228.8 g); p= 0.007. Besides, 61% of children of women with GD were obese vs 54.1% of children of non-GD women, although this difference was not statistically significant.
Conclusions: Prevention of GD could be a strategy of preventing obesity in childhood and adolescence.

P3-d2-1275 Fat Metabolism, Obesity 14

Changes of body composition indicators in pubertal children with alimentary obesity

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Background: Obesity is a worldwide pathological epidemic. Children and adolescents are a major concern in this trend.
Objective and hypotheses: To identify the dynamics of body composition in children with alimentary obesity in puberty.
Methods: 22 children with alimentary obesity with body mass index over 30 kg/m2 were examined. Anthropometric parameters (height, weight, waist and hips circumference (WC, CH)), body mass index (BMI), biochemical parameters (Ca^{2+}, Mg^{2+}, P) were analyzed. Bone mineral density (BMD) were measured by dual x-ray absorptiometry (DXA). Depending on the stage of puberty 2 groups were identified: 1st group - with early puberty (2-3 Tanner stage) (boys/girls = 6/4, age 13,7±0,9 years, and 10,6±0,2 years); and 2nd group - with late puberty(4-5 Tanner stage) (boys/girls = 7/5, age 15,8±0,2 years, and 13,8±0,6 years).

Results: An increase of BMI in puberty: in first group was 32,3±0,5 kg/m² in boys and 31,7±0,7 kg/m² in girls; 35,6±0,9 kg/m² and 34,3±1,9 kg/m², respectively, in second group (p< 0.05). Body weight was 87,5±4,9 kg for boys and 68,3±2,9kg for girls in first group, 109,9±1,9 kg and 87,4±7,5 kg, respectively, in second group (p< 0.05). Levels of ionized calcium, 1,07±0,02 mmol/l and ionized magnesium 0,41±0,01 mmol/l in first group in boys were decreased, levels of phosphorus were within normal range 1,4±0,06 mmol/l. Indicators of BMD in first group were 1,19±0,04 g/cm² in boys and 1,03 ± 0,04 g/cm² in girls, 1,24±0,01 g/cm² and 0,84±0,17 g/cm², respectively, in second group (p< 0,05). Age and sex differences in Z-scores were not observed (p< 0.05). In the second group the percentage of fat decreased with increasing lean mass in boys; total fat mass, free fat increased in girls (p> 0.05).
Conclusion: Decreased levels of Ca2 +, Mg2 + in boys with alimentary obesity at age 13,7±0,9 years may lead to future deficiency of BMD. Further research needed.

P3-d2-1276 Fat Metabolism, Obesity 14

Metabolic syndrome in obese Peruvian adolescents 10 to 16 years of age, attending the Instituto Nacional de Salud del Niño in Lima - Peru

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Background: Obesity in young people is on rise not only in developed countries but also in developing countries. It is considered the epidemic of the 20th century. It should be considered as the chronic disease with excessive accumulation of body fat, wiich is hazardous to health.
Objective and hypotheses: To determine the prevalence of metabolic syndrome (MetS) in children of both sexes.
Methods: A descriptive, retrospective, observational, cross-sectional study. The universe of the study was 3457 medical records of children of both sexes, aged between 10 and 16 years who presented to the Endocrinology Unit of the Instituto Nacional de Salud del Niño(INSN) during 2005-2010; 2806 met the requirements for inclusion in the study. The sample size was calculated and added 10%, total medical histories examined were 319. The selected records were evaluated according to the criteria of the NCEP ATP III and the IDF criteria for diagnosis of metabolic syndrome in pediatric population. The descriptive variables were expressed in frequency and percentages.
Results: The results showed 34.2% of patients with MetS, according to the diagnostic criteria of the NCEP ATP III (52.3% male and 47.7% female) and 27.3% according to the IDF (57.5% of male and 42.5% female). Risk factors most frequently encountered were: hipertrigliceridemia ≥ 150 mg / dL (NCEP ATP III: 90.6%, IDF: 83.3%), HDL-C ≤ 40mg/dL: NCEP ATP III: 43.3% , IDF 91.4%), hypertension (ATP III: 43.3%, IDF 17.2%), blood glucose> 100 mg / dL (NCEP ATP III 12.9%, IDF 20.5%).
Conclusions: The present study reveals a comparable prevalence of metabolic syndrome to work most far reported worldwide. The most frequent MetS major criteria were: obesity, hipertrigliceridemia, and decreased HDL-cholesterol. When comparing the ATP III criteria and the IDF criteria for the evaluation of metabolic syndrome in adolescents, these are lower in the latter than in the former ones.

P3-d2-1277 Fat Metabolism, Obesity 14

Endocrine disorders in a series of Prader-Willi syndrome patients

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Background: Prader Willi syndrome is known as the most prevalent syndromic obesity. The associated high morbidity and mortality, is, in all probability, a result of morbid obesity. Several endocrine dysfunctions are traditionally described in Prader-Willi patients, suggesting hypothalamic-pituitary disturbance.
Objective and hypotheses: To evaluate endocrine dysfunction in a series of Prader Willli patients from across Romania.
Methods: A series of 12 patients, including children and young adults with the diagnosis of Prader Willi Syndrome, confirmed trough either methylation of FISH method.
Results: The medium age was 12.5 years, with the age range between 2 and 28 years, 25% were boys and 75% girls, median BMI-Z score was +4.11, all patients were obese (International Obesity Task Force 2000 criteria). We found growth hormone deficiency in half of patients and 66% of them had growth hormone treatment. Hypogonadism was present in two patients, and hypothyroidism in other two. We found insulin resistance in two patients, while diabetes mellitus was detected in 2 patients, one treated with oral antidiabetic medication and another one with insulin. One patient deceased at age 28, due to cardiovascular complications.
Conclusions: Prader-Willi syndrome is a disabling condition associated with endocrine disorders like insulinresitance, diabetes mellitus, GH deficiency, hypogonadism and hypothyroidism. Weight management and a concentrated strategy for treatment of these endocrine disorders is likely to improve the health and quality of life in affected individuals.

P3-d2-1278 Fat Metabolism, Obesity 14

Correlation between level of 25(OH)D and body mass index in adolescents in Manado

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Background: Worldwide data reported high incidence of vitamin D deficiency and insufficiency. Location, polution, life style, and adiposity are factors that affect the level of vitamin D, but whether the increasing body mass index correlated with vitamin D level in adolescents was rarely studied.
Objectives: To know the correlation between level of 25(OH)D and body mass index in adolescents.
Methods: This is a cross sectional study of 76 adolescents. Level of 25(OH)D categorized as sufficient if ≥ 30 ng/ml, insufficient if 10 - 30 ng/mL, and deficiency if < 10 ng/mL. Level of 25(OH)D and nutritional status was analyzed using t test, and the correlation between level of 25(OH)D and body mass index was analyzed using Pearson test. It considered significant if p < 0.05.
Result: From 76 adolescents (32 boys and 44 girls), 38 adolescents were well nourished and 38 adolescents were obese. Vitamin D insufficiency were found in 88,15% adolescent, and 47,36% of them were obese. There were 1 obese adolescents with vitamin D deficiency (1,3 %). There is significant difference of 25(OH)D between obese adolescents and well nourished adolescents (p < 0.001), and there is negative correlation between vitamin D and body mass index (r = - 0.363; p = 0,001).
Conclusion: Incidence of vitamin D insufficiency in adolescents in Manado is high. Higher body mass index correlated with lower vitamin D levels. Physician should be aware to give vitamin D supplementation for adolescents, especially one with high body mass index.

P3-d2-1279 Fat Metabolism, Obesity 14

Abstract has been withdrawn

P3-d2-1280 Fat Metabolism, Obesity 14

The importance of weight loss in treating PCOS in an adolescent girl

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Introduction: PCOS is the most common hormonal disorder in women and the most common cause of amenorrhea.
Aim: To present PCOS teenager and her successful non-pharmaceutical treatment.

Case description: 14 years and 4 months teenage girl was seen at the OPC for secondary amenorrhea. She had menarche at 12 yrs and 10 mos old and had only had 1 menstruation period since. Suffering from obesity since the age of 9 years old. Clinical examination: HT: 161,5 cm (90-95th percentile), BW: 81,2 Kg (> 95th percentile), BMI: 31., BP: 121/100 mmHg (10th / > 95th percentile), WC: 102 cm

Breasts, axillae, pubic hair Tanner stage V, Skin: Acanthosis nigricans, Hirsutism FERRIMAN GALLWEY SCORE 13 .Laboratory findings: DHEA-S: 4,230 (0.7 to 3.9 n.v.), T: 0,641 ng/ml, E2: 44,06 pg/ml, Prl: 332.6 mIU/ml, LHRH stimulation test: LH / FSH = 6,5 HbA1c: 5.4%, OGTT: glucose within normal limits, significant degree of insulin resistance. HOMA-IR: 2,26

Pelvic U/S: Typical picture of polycystic ovaries.

Treated with increased physical activity, 2-4 hours per week of aerobic exercise of moderate intensity and maintaining a strict diet program. Compliance was exemplary and resulted in progressive weight loss, reappearance of menstruation periods, resolution of signs of hyperandrogonaimia. Menses resumed after 5 months, when BMI was 26.9, and in OGTT 0min: G:72 mg/dl and Ins: 7.5 μIU/ml, and in 120min

G: 89 Ins :110 μIU/ml. Two years later her BMI is 24.2 and she has normal cycle.

Conclusions: The treatment of obesity and insulin resistance with diet and increasing physical activity may be the treatment of choice for obese teenage girls with PCOS.

P3-d2-1281 Fat Metabolism, Obesity 14

Carotid intima-media thickness, gender and age distribution in obese children

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Background: Carotid intima media thickness cIMT,ultrasound (US) measurement from the common carotid arthery in children is useful tool in screening risk factors for CVD.Increased prevalence of high risk children for subclinical atherosclerosis in obesity, dyslipidemia and diabetes,with growth trend CVD risk factors,indicate using reliable and reproducibile method for dethermining cIMT. Detection in early stages of atherosclerotic process by US as useful tool is possible trough use of trained person and quality equipment. Data analysis using noninvasive assessment is a great help to medical providers in prevention vascular complication.

Objective and hypotheses: Evaluate relation cIMT and BMI according the gender and age in obese children.

Methods: US was performed with Vivid system, by US diagnostic profetional. Including criteria was obese children from 10 to 17 age, group I BMI P 90 to 97, group II BMI over P 97, with evaluated lipid status (dyslipidemia, atherogenic index)

Results: Data colected from 74 pediatric patients, high BMI 45% according age, 68% according gender, more from 12 to 15 age, find 21 f, 14 m, with cIMT med 0,7(0,6 to 1,1mm). Positive corelation cIMT /BMI at older f. At m, higher cIMT/ and age not corelate. In group I no gender diffrence. In group II more change cIMT in f.

Conclusions: EASO guide propose evaluation comorbidity before obese diagnosis.Explore cIMT in ekces BMI children, adolescents, show positive risk for CVD. Detection elevated cIMT is important tool for planing needs for obese therapy instruments.

P3-d2-1282 Fat Metabolism, Obesity 14

Neonatal hypotonia as an indicative for early diagnosis of Prader-Willi syndrome

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Background: Prader-Willi Syndrome (PWS) is a multi-system disorder resulting from the lack of expression of the imprinted of the paternal allele in the 15q11-q13 region.

Objective and hypotheses: To retrospectively analyze the phenotypical and genetic features of this syndrome.

Method: We report the cases of PWS diagnosed in the reference hospital for our Community between 1991 and 2012.

The genetic diagnosis was made using FISH techniques, methylation analysis, MLPA and/ or micro-satellite study of the 15q11-q13 region.

Results: Seven patients with SPW were identified, yielding an estimated incidence for the study period of 4.0/100,000. Mean age at diagnosis was 7.2±10.1 years, with clear improvement in the last 2 years (0.48±0.08 years). The clinical sings leading to diagnostic suspicion were hypotonia (43%), obesity (29%), and psychomotor delay and genital hypoplasia (28%). A genetic study was requested before the age of two years in 57% of the cases.

Four of the seven cases (57%) exhibited uniparental disomy, two displayed a maternal chromosomal deletion (29%), and one (14%) presented an alteration at the center of the imprint. On two occasions, the first genetic study (FISH) was negative, later confirming [diagnosis] with new study techniques (methylation/MLPA).

Endocrinological abnormalities presented were obesity (75%), growth delay (100%), and diabetes (in a single case). Three patients were treated with HGH; one of them with early onset.

Conclusions: The genetic cause most often associated with PWS in our population is uniparental disomy.

Improved genetic techniques have made earlier diagnosis and early, multidisciplinary treatment possible, which demands strict control over time.

Neonatal hypotonia is a key sign in diagnosing this syndrome; in line with the new Gunay-Aygun diagnostic criteria, genetic testing in the first year of life should have been ordered for 100% of our patients.

P3-d2-1283 Fat Metabolism, Obesity 14

Comparative assessment of metabolic syndrome incidence in obese adolescents

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Background: The work was initiated to comparatively assess metabolic syndrome (MS) incidence in obese adolescents in accordance with the European waist circumference (WC) percentile charts and WC percentile charts for Uzbek population.

Methods: We examined Uzbek 80 adolescents with exogenous constitutional obesity (ECO) aged from 10 to 16, 45 (56.3%) boys and 35 (43.7%) girls among them. Mean age was12.7±0.19 years. Assessment of WC distribution in the representative sample was performed in 2456 Uzbek healthy children aged from 7 to 18, 1231 (50.1%) boys and 1225 (49.9%) girls among them. MS was diagnosed in accordance with IDF criteria (2007).

Results: On the basis of IDF criteria (2007) WC component of MS syndrome was ≥ 90 percentile in 76 (95%), according to WC percentile charts for Uzbek population being the one in 100% (n=80). In compliance with the European WC percentile charts for children and adolescents [Fernández J., 2004] MS was diagnosed in 27 (33.7%) adolescents, MS incidence as per WC percentile charts for Uzbek children and adolescents being 30 (37.5%) cases. Triglyceride (TG) level was ≥ 1.7 mmol/l in 56 (70%) patients with ECO; HDL concentrations being < 1.03 mmol/l in 26 (32.5%). Fasting glycemia was ≥5.0mmol/l in 11 (13.8%) of patients with ECO. Systolic arterial pressure ≥130 mm Hgwas found in 6 (7.5%) patients and diastolic arterial pressure ≥85 mm Hg being registered in 9 (11.3%).

Conclusions: The findings from our study confirmed the necessity to develop WC percentile charts for various ethnic groups to help register incidence of

MS and its components in children and adolescents with ECO.MS diagnosis has been optimized on the basis of the WC percentile charts developed for Uzbek adolescents, its incidence being found 36.3%.

P3-d2-1284 Fat Metabolism, Obesity 14

The prevalence of obesity and overweight in children and adolescents

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Background: Obesity is a chronic disease leading to serious problems with health. In most cases it starts at child's age.
Objective and hypotheses: To establish the prevalence of obesity and overweight in children and adolescents.
Methods: There were examined 10000 children and adolescents at the age from 10 up to 16 years (5023 boys, 4977 girls). A child be diagnosed as overweight if body mass index (BMI) is in at least the 85th percentile but less than the 95th percentile, and as obese if BMI is in at least the 95th percentile for age and sex. Normal standards of Cole T.J. (2000) were used. Statistical significance of differences between groups was estimated by χ^2 criterion.
Results: The prevalence of overweight amounted to 8.6%, while of obesity - to 6.3%. The prevalence of overweight in boys and in girls was equal (8.6% and 8.4%, respectively), whereas obesity was observed in boys 1.5 times more often than in girls (7.6% and 5.0%, respectively, $\delta < 0.001$).In boys at the age of 10-14 years overweight occurred more often than at the juvenile period (9.6% and 6.3%, respectively, $\delta < 0.001$). A similar tendency was also revealed in girls. The prevalence of overweight at the age of 10-14 years amounted to 10.3%, whereas at the age of 15-16 years - only to 3.7% ($\delta < 0.001$). The age differences in the prevalence of obesity turned out to be non-significant. In boys at the age of 10-14 years it was recorded in 8.0%, while at the age of 15-16 years - in 6.8% of the examinees. In girls of the same age groups, obesity occurred in 5.3% and 4.5% of cases, respectively.
Conclusions: The prevalence of overweight in children of school age amounted to 8.5%, of obesity - to 6.3%. In boys the obesity was recorded 1.5 times more often than in girls both at the age of 10-14 years and in adolescents. These parameters exceed more than 10 times the data of official statistics, according to which the prevalence of obesity does not exceed 0.5%.

P3-d1-1285 GH and IGF Physiology and Treatment 7

Growth hormone treatment of patients with Fanconi anaemia after hematopoietic cell transplantation

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Background: Short stature is a common feature of Fanconi anemia (FA) and is frequently due to growth hormone deficiency (GHD). Except for a single case report, there are no data on the effectiveness of recombinant human growth hormone (GH) treatment in FA patients who underwent hematopoietic cell transplantation (HCT).
Objective and hypotheses: The goal of this study was to evaluate the response to GH treatment in FA children after HCT. We hypothesized that height SDS will increase by at least 0.5 in response to therapy.
Methods: This was a retrospective study that included 4 FA patients (2 males) who had a HCT at a mean age of 8.8 ± 2.2 years after which they received GH treatment for at least 3 years and were now near adult height.
Results: All patients had GHD. The mean age at initiation of GH was 10.2 ± 2.0 years. Patient 1 had an ectopic pituitary gland and patient 3 had a pituitary microadenoma. Patient 4 had primary ovarian failure and was treated with estrogen replacement. The mean dose of GH was 0.28 ± 0.1 mg/kg/week. During the first year of therapy, growth velocity increased from 4.0 ± 1.1 cm/year (-2.2 ± 1.8 SD) to 8.7 ± 3.3 cm/year (4.2 ± 3.0 SD). The mean change in height SDS was 0.9 ± 0.6 over an average treatment duration of 4.9 ± 1.6 years. None of the patients experienced adverse events from GH.

	Pre-treatment data					Treatment data at last visit			
Patient	Age (yr)	Sex	Bone age (yr)	Tanner stage	Height SDS	Age (yr)	Bone age (yr)	Tanner stage	Height SDS
1	7.7	M	7.0	1	-2.5	14.9	16	4	-1.4
2	9.7	F	6.8	1	-2.7	13.7	12.5	4	-2.1
3	11.1	M	11.5	1	-1.9	15.3	17	5	-0.3
4	12.3	F	11.0	1	-2.0	16.3	14	4	-1.7

[Patient characteristics]

Conclusions: In this series of four FA patients, GH treatment was well tolerated and resulted in an increase in height SDS of at least 0.5 in three out of four patients. The patient who showed a less robust response was the oldest and had primary ovarian failure.

P3-d1-1286 GH and IGF Physiology and Treatment 7

Analysis of efficacy and security of long-term GH treatment in small for gestational age patients

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Background: Growth Hormone has proven its efficacy in children born small gestational age (SGA), but with a highly variable response. It is therefore crucial to better understand the clinical and biological parameters underlying this variability.
Objective and hypotheses:
1.- To evaluate GH treatment response according to different variables.
2.- To investigate safety of GH treatment on carbohydrate metabolism.
Methods: Retrospective review of 78 children (33 males) children with SGA that was treated according the EMA criteria. We used as indicator of efficacy of therapy the changes in height (sds) until four years and as indicator of security the insulin sensitivity the changes in glycemia and Homeostasis model assessment (HOMA) levels.
Results: At the study initiation, age (mean ± SD) was 5,8 (1,1) years, height sds -3,03 (0,68). 13 Patients has started puberty at 4th year of treatment. The mean sds birth weight was -2,21 (1,15) and birth length -2,72 (1,1). Mean sds target height was -1,19 (0,76).Mean gain of sds height was 0,55 (0,46) and 1,42 (0,7) after 1 and 4 years respectively. The sds height after 4 years was correlated with initial age (p= 0,03) and height (p= 0,02).A mild increased of HOMA was observed after one year: 1,12 (1,2) to 1,32 (1,4) and after four year: 1,97 (1,4). However, after a paired analysis we did not found significatives differences. There was a significant relation between the HOMA increased and age at treatment start (p=0,017) and the height gain after one year (0,017).One patient developed a type 2 diabetes in the third year of treatment and the GH was retired, and then the OGTT was normalized.
Conclusions:
1.- Age and height initials were mild predictors of height gain at 4th year of treatment.
2.- There was a mild association between increased of HOMA and height gain.

P3-d1-1287 GH and IGF Physiology and Treatment 7

Final height in Silver-Russell syndrome (SRS) patients treated with growth hormone (GH)

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Background: Silver Russell Syndrome (SRS) is characterized by intrauterine growth retardation, short stature and a peculiar appearance (frontal bossing, small triangular facies, downturning of corners of mouth, and asymmetry). Hypomethylation of the imprinting control region 1 on chromosome 11p15 (ICR1) and maternal uniparental dysomy (mUDP) for chromosome 7 are found in up to 60% and 10% of patients with SRS respectively.
Mean adult height in SRS is 151.2 cm (SD -3.7) for males and 139.9 cm (SD -4.2) cm for females. There is some evidence that SRS patient response to GH treatment is worse than in other small for gestational (SGA) cases, specially in those with ICR 1 alterations.

Genetic defect	mDUP7	mDUP7	Hcr11	idiopathic
Age start to treatment (years)	6.6	8.7	9.5	4.5
Chronological age-bone age (years)	0	4	3.5	3.3
Height (SDS) Start to treatment	-3.11	-4.16	-4.2	-3.92
Age at puberty onset (OP)	9,66	11.5	12.4	9
Height (SDS) at puberty onset (SDS)	-2.04	-2.31	-2.08	-2.15
Improvement of height until puberty(SDS)	1.07	1.85	2.12	1.77
Chronological age- bone age at puberty onset (OP)	-2	4	2.4	3
Age at finish GH treatment	14.2	15.8	16.45	12.9
Height at finish of GH treatment (SDS)	-2.83	-2.61	-2.54	-2.28

[Tabla. Final height in SRS]

Comments:
1. Final height is similar independent of genetic defect.
2. The improvement of height until onset of puberty was between 1 and 2 SDS.
3. The age of onset of puberty is normal in all of the patients.
4. GnRHa could be associated perhaps to improve final height.
5. All patients are satisfied with the treatment, despite the short final stature obtained.

P3-d1-1288 GH and IGF Physiology and Treatment 7

Development of antibodies against growth hormone (GH) during rhGH therapy in a girl with idiopathic GH deficiency: a case report

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Background: Since the 1980s, recombinant human GH (rhGH) has been used to treat children with GH deficiency (GHD) and growth failure. In the past, a high incidence of anti-GH antibody development in patients treated with first generation formulations of rhGH was reported. More recently, improvements in recombinant DNA technology have led to rhGH formulations with low antigenicity and rarely do patients treated with rhGH develop antibodies.
Case report: A 12.5-year-old Italian girl was referred to our Institute for progressive growth failure from the age of 6 years, with a height of 128.2 cm (-3.37 SDS) and bone age of 9 years.
Results: Endocrinological evaluation revealed a partial growth hormone deficiency (GHD) and GH therapy was started at the dosage of 0.25 mg/kg/week, with a commercially available rhGH. During the first three years, she showed an increase in growth rate and experienced pubertal development onset. Then, a poor growth rate (2 cm/years=0.43 SDS) was observed notwithstanding an increase in GH dosage (0.35 mg/kg/week) and good compliance. We found a positive anti-GH antibody titre (1:1850, cut-off 1/100), confirmed six months later (1:2035); the antibodies had low binding capacity (0.63 µg/ml), only partially capable of inhibiting the GH effect. However, GH treatment was discontinued and after three months the antibody titre decreased (1:950).
Conclusions: In conclusion, we suggest evaluation of anti-GH antibodies in GH treated idiopathic GHD children in whom growth response decreases after some years of therapy.

P3-d1-1289 GH and IGF Physiology and Treatment 7

Long-term metabolic effects of two growth hormone (GH) doses in short Japanese children born small for gestational age (SGA)

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Background: In short European children born SGA, long-term GH therapy increases height towards normal and positively affects metabolic parameters.
Objective and hypotheses: To assess the metabolic effects of long-term GH therapy in short Japanese children born SGA.
Methods: 65 children born SGA (age 3-< 8 y) received 0.033 mg/kg/day (n=31; 64.5% male; mean age 5.34 y; height SDS [HSDS] -3.00) or 0.067 mg/kg/day (n=34; 58.8% male; mean age 5.27 y; HSDS -2.83) GH for 5 y. Change from baseline was recorded for IGF-I SDS, IGFBP-3 SDS, HbA_{1c}, glucose, insulin, cholesterol (total, LDL-c, HDL-c), blood pressure and BMI. Treatment differences
(0.067-0.033 mg/kg/day) (baseline to 5 y) were analysed using ANOVA (mean [95% CI]); significance, $p< 0.05$.
Results: Mean increase in HSDS during GH treatment was significantly greater ($p< 0.0001$) with 0.067 than 0.033 mg/kg/day (0.82 [0.51, 1.13]). Change from baseline was significantly greater with 0.067 mg/kg/day for IGF-I but not IGFBP-3; both remained within normal limits (Table). Cholesterol and HDL-c decreased with 0.067 and increased with 0.033 mg/kg/day. In both groups BMI increased towards normal; LDL-c decreased; insulin increased; glucose was almost unchanged and HbA_{1c} increased but remained in the reference range (Table).

	0.033 mg/kg/day			0.067 mg/kg/day			Treatment difference (95% CI)
	Baseline	5 years	Change	Baseline	5 years	Change	
BMI (kg/m2)	14.42 (1.26)	15.24 (1.53)	0.81 (1.18)	14.16 (1.24)	15.48 (1.47)	1.31 (1.38)	0.50 (-0.14, 1.14)
Cholesterol (mg/dL)	166.9 (29.8)	168.2 (31.8)	1.3 (31.6)	181.4 (24.2)	167.6 (25.4)	-13.9 (20.2)	-15.1* (-28.2, -2.1)
LDL-c/HDL-c (mg/dL)	94.8/56.9 (26.2/9.6)	90.4/62.5 (28.4/15.6)	-4.5/5.5 (23.4/12.4)	104.7/61.9 (25.0/12.0)	89.3/61.7 (20.0/12.8)	-15.4/-0.1 (18.3/9.8)	-11.0*/-5.7 -21.3, -0.6/-11.2, -0.2)
Glucose (mg/dL)	82.4 (10.6)	89.5 (7.9)	7.1 (13.3)	78.2 (11.5)	86.1 (7.9)	7.9 (11.7)	0.7 (-5.5, 7.0)
HbA_{1c} (%)	4.76 (0.29)	4.94 (0.19)	0.18 (0.23)	4.66 (0.19)	4.98 (0.21)	0.32 (0.18)	0.14 (0.04, 0.24)
Insulin (mcU/mL)	3.4 (2.0)	9.4 (6.1)	6.0 (6.5)	3.1 (2.1)	8.8 (4.9)	5.7 (4.4)	-0.3 (-4.2, 3.5)
IGF-I SDS	-0.75 (1.06)	0.77 (1.18)	1.51 (1.43)	-0.63 (1.21)	1.74 (1.48)	2.37 (1.33)	0.86* (0.17,1.54)
IGFBP-3 SDS	-0.19 (1.18)	0.81 (1.44)	0.99 (1.84)	0.11 (1.48)	1.24 (1.62)	1.14 (1.63)	0.14 (-0.72,1.00)

*[Mean (SD) metabolic and treatment effects. *p<0.05]*

Conclusions: Long-term GH therapy in short Japanese children born SGA was associated with a dose-dependent increase in HSDS, positive changes in BMI and lipid levels, and no negative effects on carbohydrate metabolism.

P3-d1-1290 GH and IGF Physiology and Treatment 7

Investigating growth hormone deficiency (GHD): is our practice evolving?

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Background: The diagnosis and treatment of GHD during childhood and adolescence are the subject of much controversy. In the year 2000, the GH Research Society (GRS) released a consensus statement for standardising the diagnosis of GHD.
Objective and hypotheses: We investigated whether the GRS guidance has influenced practice at our institution.
Methods: Retrospective review of all children who had GH stimulation tests (GHST) from 2000-01 and 2010-11 at a single tertiary paediatric centre. GHD was defined as GH peak < 6ug/L.
Results: 38 children underwent GHST in 2000-01 compared to 85 children in 2010-11 (124% increase). There was a trend toward investigating younger patients in the latter cohort (median 10.74 vs 8.45 years, p=0.074). Median height SDS at presentation in the first and second cohort was -2.5 (IQR -3.4, -2.2) and -2.9 (IQR -3.7, -1.9), respectively (NS). A higher number of cases tested had GHD in the second cohort (67%) compared to in the first cohort at 50% (p=0.06). MRI scanning was performed in 18% and 68% of all children undergoing GHST in 2000 and 2010, respectively. Of patients found to be GHD, only 5 (19%) had MRI in 2000-01 compared to 43 (79%) in 2010 (760% increase). In the 2010-11 cohort, 23% of GHD patients who had MRI had a pituitary abnormality. The presence of an ectopic posterior pituitary, a small anterior pituitary abnormality or an interrupted pituitary stalk on MRI was highly sensitive (100%) but not specific (29%) for GHD.
Conclusions: GHST is an increasingly common test in our institution without any clear change in auxological selection criteria. In addition, our diagnostic yield of GHD has increased. The use of MRI in the evaluation of GHD has increased seven-fold and there is a need to define the timing of performing the MRI in the diagnostic pathway for GHD.

P3-d1-1291 GH and IGF Physiology and Treatment 7

Effect of zinc supplementation on growth hormone-insulin growth factor axis in short Egyptian children with zinc deficiency

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Background: The relationship between zinc (Zn) and growth hormone-insulin growth factor (GH-IGF) system and how Zn therapy stimulates growth in children has not been clearly defined in humans.
Objective and hypotheses: To assess GH-IGF axis in short children with Zn deficiency and to investigate the effect of Zn supplementation on these parameters.
Methods: Fifty pre-pubertal Egyptian children with short stature and Zn deficiency were compared to 50 age-, sex-, and pubertal stage- matched controls. All patients were subjected to history, auxological assessment and measurement of serum Zn, IGF-1, insulin growth factor binding protein-3 (IGFBP-3); and basal and stimulated GH before and 3 months after Zn supplementation (50 mg/day).
Results: After 3 months of Zn supplementation in Zn-deficient patients, there were significant increases in height standard deviation score (SDS, P = 0.033), serum Zn (p< 0.001), IGF-1 (P< 0.01), IGF-1 standard deviation score (SDS,p< 0.01) and IGFBP-3 (P = 0.042). Zn rose in all patients but reached normal ranges in 64 %, IGF-1 levels rose in 60 % but reached normal ranges in 40 % and IGFBP-3 levels rose in 40 % but reached reference ranges in 22 %. Growth velocity (GV) SDS did not differ between cases and controls (p = 0.15) but was higher in GH-deficient patients than non-deficient ones, both having Zn deficiency (p = 0.03).
Conclusions: Serum IGF-1 and IGFBP-3 levels were low in short children with Zn deficiency, and increased after Zn supplementation for 3 months but their levels were still lower than the normal reference ranges in most children; therefore, Zn supplementation may be necessary for longer periods.

	Before Zn	After Zn	z	p
Height SDS	−3.12 ± 0.2 (−2.15- -4.21)	−1.87 ± 0.1 (−2.0- -3.11)	6.76	0.033*
BMI SDS	-1.77 ± 0.41 (-2.10- -0.78)	-1.58 ± 0.32 (-0.91- -1.95)	1.80	0.26
Serum Zn (µg/dl)	56.76 ± 7.9 (37.52-93.11)	148.25 ± 15.4 (77.55-226.13)	8.29	<0.001**
Peak GH after insulin stimulation (ng/ml)	10.65 ± 2.01 (7.61-13.20)	12.10 ± 1.13 (8.90-14.82)	2.10	0.081
Peak GH after clonidine stimulation (ng/ml)	11.14 ± 1.41 (6.92-14.11)	12.99 ± 1.22 (8.90-14.82)	1.15	0.090
IGF-1 (ng/ml)	96.72 ± 11.5 (36.52-115.69)	177.50 ± 9.06 (42.65-213.66)	7.12	<0.010**
IGF-1 SDS	-2.46 ± 0.11 (-3.22- +0.55)	-0.91 ± 0.43 (-2.95 - +1.10)	9.16	<0.010**
IGFBP-3 (ng/ml)	2436.12 ± 392 (1195.45-3898.15)	2856.30 ± 411 (1341.10-3912.51)	5.90	0.042*
Bone Age SDS	-1.7 ± 1.14 (-2.44 - +0.22)	-1.5 ± 1.21 (-2.10- + 0.65)	0.13	0.35

[Data of cases before and after zinc supplementatio]

P3-d1-1292 GH and IGF Physiology and Treatment 7

Optimizing growth hormone therapy by dose titration in short children born small for gestation age

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Background: Although growth hormone (GH) therapy is increasing utilized in the management of small children born small for gestation age (SGA), optimum dosing schedules are not yet established. Children who continued receiving 57 µg/kg/day GH in year 4 had significantly greater height gain than those receiving 35 µg/kg/day GH.
Objective and hypotheses: To optimize GH therapy, we used a dose up regimen, starting at the initiation dose (0.23 mg/kg/week) of GH therapy in 10 pre-school children (5 male, 5 female, mean age 3.2 yr, range 3.0-4.5). They were with a birth weight and height below 10th percentile for gestational age, and birth weight or birth height that was < -2.0 SDS for gestational age. Their pubertal stage was on Tanner stage 1. Their height velocity SDS at 1 year before the start of GH treatment was below 0, and they were subjects with a peak GH level > 6 ng/ml in a GH stimulation test.
Methods: Serum insulin-like growth factor 1 (IGF-1) was measured at the visit to out-patient clinic. They were received the dose of GH increased if height velocity were below 0.5 cm/month after a few months treatment to achieve a serum IGF-1 level between the median and the upper end of the age-related reference range. IGF-1 values were converted into SD scores (SDSs). (nordiFIT ver.3.0)
Results: The GH dose reached 0.34 mg/kg/week in the first year. Height gain of all patients were over 6.2 cm/year and five patients whose IGF-1 SDSs were over 1.47 caught more than 7.8 cm/year height. In one patient using 0.27 mg/kg/week of GH, the IGF-1 score was unexpectedly too high. We reduced the GH dose but the height velocity had not worsened. Mean body mass index percentile was improved to 21.7 from 18.7.
Conclusions: As hypopituitary adults, the titration regimen adjusting by IGF-1 SDS might be effective in SGA, especially GH resistant children for safe GH therapy.

P3-d1-1293 GH and IGF Physiology and Treatment 7

Two cases of maternal uniparental disomy of chromosome 14 presenting with scoliosis during growth hormone therapy

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Background: Maternal uniparental disomy for chromosome 14 (mUPD14) is a disorder occurring because of the expression of imprinting gene abnormality present in the chromosome 14q region. mUPD14 results in neonatal hypotonia, small hands, poor sucking, and early onset of puberty that can be followed by shortness in stature in small for gestational age (SGA) patients. These patients present with both prenatal and postnatal growth retardation. However, the safety and the efficacy of growth hormone therapy (GHT) for this syndrome is unclear. We report 2 mUPD14 cases who were SGA and received GHT.
Case 1: A 1-year-old girl (weight, 1,858 g [-2.6 SD]; length, 45 cm [-3.4 SD]) born at 40 weeks gestation showed postnatal growth failure, poor sucking, and small hands and was diagnosed with mUPD14 at 1.8 years of age. GHT was initiated at 3.0 years of age (80 cm, -3.1 SD), and catch-up growth occurred (increased by 6.0 to 8.4 cm/year). However, GHT was discontinued after 1.2 years because of advanced scoliosis. Cobb's angle between Th6 and Th10 was 27°, and she required to wear a corset.
Case 2: A 3.4-year-old girl (weight, 2,140 g [-3.1 SD]; length, 48 cm [-2.6 SD]) born at 40 weeks gestation had postnatal growth failure, poor sucking, small hands, and epilepsy and was diagnosed with mUPD14 at 3.5 years of age. GHT was initiated at 4.2 years (87.5 cm, -3.0 SD), and catch-up growth occurred (increased by 4.9 to 9.6 cm/year). However, the child developed mild scoliosis during GHT.
Discussion: In both cases, catch-up growth was observed; however, scoliosis was detected during GHT. Scoliosis has been reported in mUPD14 patients without GHT, and scoliosis onset is associated with the deletion of the paternal allele in the 14q32 region. GHT may be associated with scoliosis progression.
Conclusions: Administration of GHT leads to catch-up growth in mUPD14 patients; however, the risk scoliosis development should be considered in these patients.

P3-d1-1294 GH and IGF Physiology and Treatment 7

Growth and biochemical response in short small for gestational age (SGA) children during the first year of growth hormone (GH) treatment

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Background: GH treatment is an approved short SGA children therapy to promote growth. Children born SGA represent a heterogeneous group of conditions, therefore responsiveness to GH therapy in this group may vary.
Objective and hypotheses: To assess auxological and biochemical response of short SGA children in the first year of GH treatment.
Methods: 40 short prepubertal children born SGA aged 7±2,4 years were treated with 0,033 mg/kg/day GH. Auxological data, fasting blood glucose, insulin, HbA1c, IGF-1 were assessed at baseline and after 1 year of GH treatment. Insulin sensitivity was calculated with HOMA.
Results: After 1 year treatment children increased height (Ht) SDS from -3,49±0,87 to -2,34 ±0,92. Mean Ht SDS gain was 1,1±0,57;however, gain< 0,5 was observed in 22,5% of patients. Children with first-year Ht gain< 1 SDS and >1 SDS do not differ significantly in baseline and after first year HOMA. There is also no difference between groups in baseline IGF-1 SDS and change in IGF-1 SDS after one year of treatment. After a year of treatment IGF-1 SDS were higher in children with Ht gain >1 SDS than with Ht gain< 1 SDS (-0,14±1,06 v -0,47±1,52, p< 0,05). At baseline Ht of 65% children was below -3SDS; their Ht SDS gain was higher but not significantly different from others. IGF-1 SDS levels in shorter patients (Ht < -3SDS) were higher, but not significantly different from higher patients. Severe primary IGF-1 deficiency according to EMA criteria was observed in 1 patient. Patients aged < 7 years (younger group) showed higher increase in Ht SDS after first year of treatment than the older group (1,26±0,57 v 0,83±0,46, p< 0,05). No differences in HOMA and IGF-1 levels between those age groups were observed.
Conclusions: SGA children experienced significant height gain after 1 year of GH treatment, especially when started therapy below the age of 7 years. A relatively high group of SGA GH therapy poor responders should force us to look for other forms of treatment.

P3-d1-1295 GH and IGF Physiology and Treatment 7

Cardiovascular risk factors in children with growth hormone (GH) deficiency: effect of a 12-month GH treatment

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Background: Growth hormone deficiency (GHD) in adults is associated with cardiovascular (CV) complications, including dyslipidaemia, hypertension, and atherosclerosis. At present, there are scant data on CV risk factors in children with GHD.
Objectives and hypotheses: To evaluate whether pre-pubertal children with GHD have increased CV risk factors, and whether a 12-month GH replacement therapy can improve these factors.
Methods: The study population included 20 pre-pubertal children with GHD (age: 9.3±2.3 yr; height SDS: -2.11±0.50; BMI SDS -0.77±1.04) and 18 healthy controls (age: 9.6±2.1 yr; height SDS -0.55±0.75; BMI SDS -0.58±1.37). IGF-1, lipid profile, glucose metabolism (fasting glucose and insulin, HbA1c), and ADMA levels were evaluated before and after 12-month GH treatment.
Results: At baseline, GHD patients showed significantly higher total cholesterol and LDL- cholesterol than healthy controls (Table). No differences were found in HDL-cholesterol, triglycerides and in glucose metabolism parameters. ADMA levels were significantly higher in GHD than in control children. After 12-month GH treatment, total cholesterol, LDL-cholesterol and ADMA significantly decreased in the GHD children, reaching levels comparable to controls. No changes were found in glucose metabolism parameters.

	Control group - Baseline	GHD group - Baseline	GHD group (At 12 months)	P values (GHD vs Control group at baseline)	P values (GHD group: 12 months vs baseline)
Fasting glucose (mg/dl)	75.50 ± 4.30	71.85 ± 6.70	72.61 ± 13.15	Not significant (NS)	NS
Fasting insulin (µU/ml)	7.23 ± 1.87	8.03 ± 5.68	8.00 ± 3.70	NS	NS
HOMA-IR	1.34 ± 0.43	1.4 ± 1.12	1.44 ± 0.74	NS	NS
HbA1c (%)	5.15 ± 0.22	5.23 ± 0.25	5.28 ± 0.26	NS	NS
Total cholesterol (mg/dl)	163.22 ± 18.47	176.35 ± 29.60	140.35 ± 46.88	0.004	0.028
HDL-cholesterol (mg/dl)	62.56 ± 11.98	58.30 ± 13.83	62.18 ± 13.19	NS	NS
LDL-cholesterol (mg/dl)	98.66 ± 18.49	110.66 ± 22.05	92.96 ± 31.09	0.020	0.042
Triglycerides (mg/ml)	74.78 ± 28.07	73.35 ± 41.07	76.53 ± 34.57	NS	NS
ADMA (ng/ml)	66.03 ± 20.38	97.81 ± 66.62	62.72 ± 44.23	0.002	0.016

[CV risk factors]

Conclusions: The present study showed that pre-pubertal GHD children show increased CV risk markers, and a 12-month GH treatment improves these abnormalities.

P3-d2-1296 GH and IGF Physiology and Treatment 8

Anthropometric characteristics, clinical findings, and growth hormone responses of children with bioinactive growth hormone

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Objective: The purpose of this study was to evaluate the anthropometric and clinical characteristics, and growth hormone responses of bioinactive growth hormone patients.
Methods: Patients, in whom a 20% increase from basal IGF-1 levels were achieved in the IGF generation tests, were diagnosed with bioinactive GH. The IGF generation tests were administered to those who had a height standard deviation score (SDS) of below -2.5 standard deviation (SD), and a growth rate of below -1 SD; bone age with a 2-year delay compared to their chronological age; had no systemic diseases or hypothyroidism, nutritional short stature and malnutrition; had serum IGF-1 levels of below -1 SD, and a peak GH response above 10 ng/mL in the pharmacological growth hormone stimulation test; and in whom GH was excluded.
Results: The patients had a mean chronological age of 11±2.4 years, bone age of 8.3±2.4 years, height SDS of -3.7±1.1 SD (-2.6-6.3), and an annual growth rate of 3.4 ± 1.2 cm prior to treatment. Patients were monitored for an average of 18±11 (12-48) months prior to GH therapy. Evaluation of the patients' responses to GH therapy revealed a mean height gain of 4.7±1.1 cm for the initial 6-month period, 8.7±1.8 cm for the first year, and 14.8±1.4 cm for the second year. There was significant improvement between the patients' pre-treatment height SDS, and post-treatment height SDS evaluated at intervals of 6 months.
Conclusion: In conclusion, the findings of the comprehensive present study conducted with a sufficient number of patients diagnosed with bioinactive GH revealed a male to female ratio of 1:2; that the patients had a more negative pathologically short stature than their genetic potentials for height; that they did not experience pubertal problems; and that their responses to GH therapy were good similar to that in GH deficiency.

P3-d2-1297 GH and IGF Physiology and Treatment 8

Safety profile of biosimilar growth hormone in children

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Background: The number of patients treated with biosmilar growth hormone (BGH) is increasing since its approval by the EMEA in 2006
Objective and hypotheses: To evaluate the effects of BGH in hydrocarbonate and lipidic metabolism as well as thyroid function, in children small for gestational age (SGA) and growth hormone deficiency (GHD).
Methods: We carried out a retrospective study in 4 children with GHD and 14 children SGA treated for at least 6 months with BGH. We analized age, sex; weigth, height and body index mass at the 0, 3, 6, 12 and 24 months of start treatment. Laboratory parameters: glycemia, hemoglocbin A1c, cholesterol, LDL-cholesterol, triglycerides, TSH, and free T4. We registered other adverse events or BGH disruption.
Results: All GHD children were male, the relation mele/female was 4/10 in SGA group. The height went up from -3,8 SD to - 2.43 SD, -2.39 SD and -2 SD at 6,12 and 24 months ($p < 0.05$). There was a significant rise of IGF-1; average at start 115.4 ng/ml (SD: 42.2) vs 250.2 ng/ml (SD: 170) at 6 months. There was no difference in hemoglobin A1c before (averge: 4.7% ,SD: 0.35) and after 12 and 24 months (average: 4.9, SD: 0.54 and 5.2, SD: 0.4).The average cholesterol increase respect the basal level was 8.9 mg/dl (SD: 14.2), 2.5 mg/dl (SD: 6) and 2 mg/dl (SD: 11.9), at 6, 12 and 24 months (no statistically significant :nss). The average triglycerides increase at 6,12 and 24 months after treatment was 12.9 (SD: 37), 10.7 (SD:23.8) and 13.1 (SD: 20.7) mg/dl (nss).The average TSH increase at 6, 12, and 24 months was - 0.14 (SD:1.7), -0.72 (SD: 1.2) y -1.21 (SD: 1.6) mcU/ml (nss). Free T4 average decreased after 6,12 and 24 months from 1.2 ng/dl to 1, 0.8 y 0.9 ng/dl ($p < 0.05$).
Conclusions: There's a significant height improvement in children treated with BGH. BGH has an adequate hydrocarbonate-lipidic metabolism and thyroid function safety profile in short and medium term. We need more studies with more patients and prospective design.

P3-d2-1298 GH and IGF Physiology and Treatment 8

Growth hormone testing - reducing the need for a second test for the diagnosis of isolated growth hormone deficiency

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Background: The diagnosis of isolated Growth Hormone Deficiency (IGHD) is based on multiple factors: clinical, radiological and biochemical along with suboptimal peak GH levels demonstrated on dynamic testing. Recent guidance from the National Institute of Clinical Excellence (NICE; UK; 2010) advises that 2 GH stimulation tests must demonstrate a subnormal GH peak < 6.7mcg/l (20mU/l) to confirm the diagnosis of IGHD. In our centre, 3 different GH provocation tests are used: insulin tolerance, glucagon stimulation (1st line) and arginine stimulation (2nd line).
Objective and hypotheses: To see if other clinical and biochemical parameters can increase the sensitivity of GH provocation testing for the diagnosis of IGHD.
Methods: A retrospective case-review of all patients in a single centre from 2002-2012 undergoing two provocation tests, comparing those with two abnormal GH test results vs. those with one abnormal result.
Results: 107 children had 2 GH provocation tests; 41% with an abnormal 1st test had a normal GH response on retesting. Lowering the cut-off to 2.7mcg/l (~8mU/l), missed 50% of children who would have otherwise met NICE GHD criteria. In patients who failed both tests, 35.3% had a low IGF-1 and 30.0% had a delayed bone age (BA) >2 years vs. 26.5% with low IGF-1 and 20.5% with delayed BA in patients passing the 2nd test (p 0.44 and 0.45 respectively).
Conclusions: Many children failing a 1st GH stimulation test will have a normal GH peak on re-test with no absolute cutoff peak on the 1st test that predicts an abnormal 2nd test. Moreover, a significantly delayed bone age or low IGF-1 does not improve the predictive value of GH testing. As currently GH stimulation testing costs ~€1000, identification of other clinical or biochemical parameters are needed to reduce the necessity for repeat testing to diagnose IGHD.

P3-d2-1299 GH and IGF Physiology and Treatment 8

Growth hormone therapy and Legg-Calvé-Perthes disease. Casual or causal relation?

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Introduction: Legg-Calvé-Perthes (LCP) disease is one of the infrequent, but possible, adverse effects related to recombinant human growth hormone (rhGH) therapy; the cases described in the literature occur mainly in children, mostly male, with partial o total GH deficiency, or chronic renal failure. We show a five year old girl who presents a LCP disease after 6 months of GH therapy.
Case study: 4 year and 5 months girl born small for gestational age who starts rhGH
(0,035 mcg/kg/day) because of a short stature (91,5 cm, -2,6 SD). Her biological mother was addicted to intravenous drugs.
She presented genu-valgum and was followed up in Ortophedics Service since three years old.
Laboratory levels before rhGH were: IGF-1: 176 ng/ml; IGFBP-3: 4.1 mcg/ml; basal GH: 6.3 ng/ml; glycemia: 76 mg/dl; total cholesterol: 190 mg/dl; TSH: 2.02 mcU/ml; insuline: 2.7 mcU/ml; C-peptide: 0.66 ng/ml. Her bone age was 24 months, retarded in 2,4 SD.
After 5 months she complains left hip pain and slight limp. There's no history

of trauma, overstarin or fever. She relates a similar attack months before that spontaneously eased up.
The hips are asymmetric at x-ray, and nuclear magnetic resonance shows a bilateral alteration of the signal of ossification centers in the femoral head and neck of femur, spill joint , compatible with LCP disease.
Growth velocity during the rhGH treatment was 10,2 cm per year, and height after 6 months (chronological age: 4 years and was in -2,3 SD (it has risen in 0,3 SD). At this time rhGH was discontinued.
Conclusion: There are no studies referring frequency nor relation between SGA, rhGH therapy and LCP disease.
rhGH therapy should be discontinued in children diagnosed with LCP disease.
This case we show is quite rare due to the sex (less than 25% in female) and the bilateral concern (less than 10-20%).
Maternal history could determine the disease.
It's no clear if rhGH has precipitated the injury or is patho-physiological mechanism.

P3-d2-1300 GH and IGF Physiology and Treatment 8

One year treatment with recombinant human growth hormone (rhGH) in a group of children with short stature: results from the DATAC study

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Background: rhGH-boosted increased height velocity (HV) is common but variable.
Objective and hypotheses: To explore the correlation between HV and other variables at one year of therapy with rhGH in GH treatment-naïve Spanish children with short stature.
Methods: This retrospective, observational, non-randomised study included 504 children with GH deficiency (GHD) (64%), born small for gestational age (SGA) (30%) and with Turner syndrome (TS) (6%). Demographical, auxological and biochemical variables were recorded. Comparison of means (t-test for related samples; $P< 0.05$) and multiple linear regression were done. Variables with $P< 0.1$ in bivariate correlation with HV entered the regression model.
Results: Mean age at start of treatment was 8.5 years (y) in TS and SGA and 12 y in GHD children. Mean height increased significantly by 0.70 SDS for SGA, 0.64 for complete GHD with a normal MRI (cGHD nMRI), 0.57 for complete GHD with a pathological MRI (cGHD pMRI), 0.50 for TS and 0.48 for partial GHD (pGHD). Mean baseline and 1y HV (SDS) were -1.75 and 2.33 for TS, -1.43 and 2.34 for SGA, -2.92 and 3.11 for cGHD pMRI, -2.27 and 2.65 for cGHD nMRI, and -1.67 and 2.72 for pGHD, respectively ($P<$ 0.01 for every comparison). Mean dosages of rhGH (mg/kg/day) were 0.042-0.046 for TS; 0.038-0.039 for SGA; 0.032-0.035 for GHD. Mean IGF-I and IGFBP-3 in Tanner I children increased in all the groups. Variables with an independent association with HV (R^2=0.511) were target height (SDS) (B: 0.405; P=0.02), delay in bone age (y) (B: 0.253; P=0.002), and HV (SDS) at baseline (B: 0.164; P=0.002) and height prognosis (cm) (B: 0.018; $P< 0.001$).
Conclusions: In children with TS, SGA, and GHD one year of rhGH treatment was effective. The late mean age at which rhGH therapy was started is worrisome since it may hamper ultimate adult height. Half of the HV variability after hormonal catch-up was explained by target height, delay in bone age and previous HV.

P3-d2-1301 GH and IGF Physiology and Treatment 8

Growth hormone treatment in a boy with Becker muscular dystrophy

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Background: Becker muscular dystrophy is a neuromuscular X-recessive disease characterized by progressive muscle wasting. Growth failure is described in muscular dystrophies; however only a case related to growth hormone deficiency (GHD).
Case report: An eight-years-old boy referred to our Pediatric Clinic for short stature. At first evaluation he had an height and a weight of -3 SDS with a pubertal stage of 1 according to Tanner. Laboratory studies revealed: a normal thyroid and adrenal function, negative anti-endomisium and anti-tissue tranglutaminase values, and high serum levels of Aspartate aminotransferase (333 U/L) and Alanine aminotransferase (215 U/L). GH stimulation tests showed a GHD (GH peak response to arginine: 8.1 ng/mL; GH peak response to insulin: 5.4 ng/mL). Magnetic resonance imaging of hypothalamic-pituitary region and abdomen ultrasound scan were normal. GH replacement therapy was started at the dose of 0,033 mg/kg/day. Persistent high transaminase levels led to perform additional testing: measurement of α(1)-antitrypsin, ceruloplasmin, antinuclear antibody, smooth muscle antibody and the most common viruses serology were all negative. At the age of 9 the patient presented a mild weakness and leg pain, so we searched for muscle disorders: Creatine phosphokinase was 10 times higher than normal. Multiplex ligation probe amplification (MLPA) of DMD gene detected duplications of exons 16-22. The growth velocity of the patient evidenced an improvement in the first 12 months of therapy (7 cm/year).
Discussion: Endocrine management of short stature in patients affected by muscular dystrophies is complicated by their multifactorial nature; nevertheless in our experience growth hormone therapy in patients with BMD cannot be excluded and can give positive effects. However, only future long term studies will tell us if GH therapy in patients affected by MD could be appropriate without detrimental effects on neuro-muscular or cardiopulmonary function.

P3-d2-1302 GH and IGF Physiology and Treatment 8

Somatotrope axis evaluation in a group of patients with Cornelia de Lange syndrome

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Background: Cornelia de Lange syndrome (CdLS) is a rare genetic disease (OMIM # 122470) characterized by a distinctive craniofacial phenotype, growth and cognitive impairment and upper limb malformations.
As of today, only a few studies about the somatotrope axis of these patients have been carried out. Moreover, it has been hypothesized that their intrinsic growth retardation may be associated with an alteration in the growth hormone secretion or with peripheral resistance to it.
Objective and hypotheses: The aim of this study is to evaluate the hormonal somatotrope axis in a group of patients with clinical diagnosis of CdLS.
Methods: We carried out an observational, prospective study of 8 patients with CdLS (6 males, 2 females; 7 prepuberal) whose ages ranged between 2 and 14 years. One patient had severe phenotype, one mild-moderate and 7 mild. Hormonal studies included IGF-1 (ng/mL), IGFBP-3 (mg/mL), and functional evaluation of growth hormone (GH) with clonidine stimulation test and overnight GH profile. Endocrinological tests were carried out *in vitro* by

automated immunoassay using chemiluminescence.
Results: Four patients had short stature below 2 SDS (mean -1.89 SDS [-3.56, -0.94]). Stimulation with clonidine gave a response lower than 10ng/mL after stimulation in 6 out of 7 patients. Three of them had a response lower than 7ng/mL over baseline (mean peak of 6.28 ng/mL [2.33, 8.99]) without evidence of a temporal pattern of GH secretion. In seven patients the nocturnal profile of GH secretion showed values lower than 3 ng/mL/hr for the mean (mean 2.11 ng/mL/hr [1.15, 2.56]) and lower than 10 ng/mL/hr for the peak (peak 8.29 ng/mL/hr [2.84, 18.7]). Plasma levels of IGF-1 and IGFBP3 did not showed significant variations.
Conclusions: The results of this study support the hypothesis that the delayed postnatal growth of children with CdLS is caused, at least in part, by a neurosecretory dysfunction.

P3-d2-1303 GH and IGF Physiology and Treatment 8

Idiopathic growth hormone insensitivity

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Introduction: Short stature is a frequent presentation to paediatric endocrine clinics. Idiopathic short stature with normal growth hormone (GH) secretion and GH deficiency are the most common growth disorders diagnosed. Other defects within the GH/Insulin like growth factor 1 (IGF-1) signalling pathway can lead to severe short stature. These include abnormalities of the GH receptor, GH signalling, IGF1 synthesis, and IGF response (GH insensitivity or resistance).
Case study: The male patient presented at 18 months with a height of -3.2SD despite normal birth parameters (BW 4050g, BL 50cm - 90th centile, HC 35cm - 50th centile.) Growth had slowed during the second 6 months of life. Past medical history included asthma, eczema and fluctuating diarrhoea associated with eosinophillic enteritis. His parents were non-consanguineous and of normal height (mid-parental height 50th-75th centile). Examination revealed proportionate short stature, weight -3.9SD, mid-facial hypoplasia, and normal external genitalia.
Initial investigations excluded chronic disease and growth hormone deficiency; however, his Arginine/glucagon stimulation test revealed dysregulated GH release. IGF1 and IGFBP3 were undetectable and did not respond during an IGF-1 generation test. Acid labile subunit was also low (20nmol/L, NR 50-260). His IGF-1 level and his height velocity did not increase during a 6 month trial of growth hormone and he remained with a height of -3.5SD and a weight of -2.2SD at 4 years. Prolactin was measured as normal. Genetic analysis has not identified any mutations in the GHR, Stat5b, or ALS.
Conclusion: This cause of GH insensitivity is unknown in this patient. Further genetic analyses are pending, including studies of GH signalling *in vivo* using the patient's skin fibroblasts. We plan to trial rIGF-1 treatment in the future.

P3-d2-1304 GH and IGF Physiology and Treatment 8

Neurofibromatosis type I and endocrine disorders

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Background: The Neurofibromatosis type I is a pathology of hereditary autosomal dominant transmission (1/3000).
If the diagnosis is easy for adults, its recognition is often delayed in children due mainly dermatological manifestations. However, the association of endocrine disorders can sometimes make an early diagnosis.
Objective and hypotheses: We report three observations of neurofibromatosis type I i children.
Results: T. K 16 has a delay stature T < -2DS/TC associated with arachnoid cyst surgery 01 years ago. the interrogation reveals the appearance at the age of 08 years of secondary sexual characteristics and café au lait spot. The paraclinical shows central precocious puberty and optic glioma.
AL 15 years consulting for primary amenorrhea. Clinical examination noted a size to -1 DS / TC, impubérisme , multiple café au lait spots and axillary lentiginoses appeared at the age of 05 years. The record reveals hydrocephalus, hypogonadotropic hypogonadism, an optic glioma and ophthalmologic disorders AV 2/10 papillary pallor.
BA 13 years has short stature - 2.5 DS / TC, impubérisme, café au lait spots scattered appeared at the age of 05 years and axillary lentigine. The paraclinical shows elevated calcitonin baseline TcT to 50 pg / ml and after test calcium without thyroid nodule visualization.
FN is 12 years hospitalized for exploration of a left adrenal mass. Clinical examination reveals the cafe au lait spots and lentigines appeared at the age of 8 years. Etiologic is for a 70mm nonfunctional pheochromocytoma associated with nodules lish.
Conclusions: Neurofibromatosis type 1 is a serious pathology. Endocrine disorders are frequent and appearance variables. They must be recognized and treated early because of their potential severity.

P3-d2-1305 GH and IGF Physiology and Treatment 8

Metabolic impact of GH deficiency in children

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Background: The growth hormone deficiency is a cause of growth retardation in children. In adulthood, other complications arise. There is an increase in cardiovascular mortality due to an atherogenic lipid profile and glucose tolerance abnormalities.
Objective and hypotheses: Through a retrospective study, we tried to find metabolic impact of somatotropin deficiencynn in children.
Methods: 92 congenital somatotropin deficieny patients (IGH: 56 boys, 36 girls) mean age at diagnosis of 10.8 years for males (01 -19 years) and 6.5 years for females (1 - 17.5) were followed in consultation. The IGH was isolated in 63 patients, associated with a thyrotropin insufficiency in 16 cases and adrenocorticotropin insufficiency in 13 cases. All patients underwent a metabolic evaluation including fasting glucose, post prandial and lipid A and at the time of diagnosis. Mean values were compared to a control group.
Results:
Glucose: 0.773 ± 0.102 (0.75 - 0.79)vs 0.7 - 1 (DNS)
Triglycerides: 0.79 ± 0.32 (0.73 to 0.85) VS 0.5 - 1.5 (DNS)
Total cholesterol: 1.66 ± 0.32 (1.60 to 1.72)vs 1,55-1,78(P < 0.05)
HDLc * 0.503 ± 0.15 (0.47 to 0.53) vs 0,45-0,49 (DNS)
≥ 0.45 ♂
≥ 0.55 ♀
LDL 0.29 ± 1.006 (0.95 - 1.06) vs0,98- 1.10 (DNS).
Conclusions: Metabolic disturbances are not as free as adults.Abnormalities of lipid are variable in children and adolescents.
Nevertheless, a qualitative impairment in early lipoproteins (small dense LDL) is reported which requires a more specific study. atherogenic risk exists and increases with age Therefore the long-term surveillance is necessary.

P3-d2-1306 GH and IGF Physiology and Treatment 8

Growth hormone deficiency in a girl with Killian Pallister syndrome

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Introduction: Isolated growth hormone deficiency (IGHD) is most frequent pituitary disorder, mostly idiopathic, however in small proportion of cases mutations in GH or GHR genes have been detected. IGHD is rarely it is associated with other genetic conditions. Killian Pallister syndrome, conversely, is rare chromosomal disorder characterized with accelerated growth in the first months followed by the period with slow growth velocity. Also, mental retardation and specific dysmorphic features are present.
Case study: We present a girl with short stature and mental retardation. This was the first child in a family, born on time, BW 2500/45. Facial dysmorphism included coarse face, prominent forehead, sparce hair laterally, up-slanted palpebral fissures, prominent philtrum, full cheeks. Failure to thrive was noticed early. Except minor cardiac anomaly, the child had normal evaluation of other

organs. Tetrasomy 12p was detected in 30% of the cells on FISH analysis of the buccal smear. At the age of 2,5 years short stature was evident, 3,5 SDS below the mean. GH stimulation tests showed low GH, with the peak value of 4,9 ng/ml, also IGF1 and IGFBP3 were below the expected values for the age. MRI of the pituitary showed normal structure. Other pituitary hormones were normal. At the age of 4 years the child develops seizures that were difficult to cope and further regression of her mental state occurred. Therefore she was not given GH replacement therapy.
Conclusions: There are very few studies in the literature showing GH deficiency in children with Killian-Pallister syndrome. It is not clear how tetrasomy 12p in mosaic state can influence low GH values. Since most of the cases with GH deficiency remain idiopathic, further studies in the genetic causes will help to elucidate intra and extracellular mechanisms of growth. The children with KPS can give a clue for revealing some of the underlying mechanisms.

P3-d3-1307 GH and IGF Physiology and Treatment 8

The efficiency of treatment with growth hormone replacement therapy in children with idiopathic growth hormone deficiency in Albania

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Background: The idiopathic growth hormone (GH) deficiency is defined as the shortest height (-2 SD) without any further pathologies, including a detailed hormonal and radiological evaluation.
Objective and hypotheses: The evaluation of the efficiency of treatment with somatropin in children with idiopathic gh deficiency in Albania.
Methods: The study is based on the survey of 50 children of different ages, diagnosed with idiopathic GH deficiency by the pediatric endocrinology department of 'Mother Theresa' University Hospital Center, excluding those children diagnosed with Turner Syndrome, chronic renal disease, GH resistance, SGA and IUGR. We evaluated the efficiency of the 1st, 2nd, 3rd-year treatment with somatropin, and measured the height (in cm/SD), the bone age, the values of GH and IGF-1, while using the Tanner-Whitehouse and Bayley-Pinneau method for the forecast of the height.
Results: The study involved 50 children, 43 male (86%) and 7 female (14%), who have showed up at the pediatrics ward between 2001- 2009. The median period of the treatment given was 4.6 years (3-10 yrs). The height at the moment the patients were first diagnosed was 118.3 ±13.1cm; after the 1st year of treatment with somatropin, the stature reached 129.7 ± 12.6 cm; after the 2nd year 137.8 ±12.3 cm and after the 3rd year, the height reached 144.9 ±12 cm. Growth velocity in the 1st year of the treatment was 11.4 ± 2.8cm/y, in the 2nd year it was 8.14 ± 2.13cm/y, while after 3 years of the treatment's initiation it reached 26.74 ±5.4cm/y. The patients appeared to have a differentiation in height based on the Standard Deviation (SD) -4.6 SD ±1.2. The first year of the treatment saw an improvement in the patients' statures, with a SD of -3.4 ± 1.3 and it was found the most beneficial.
Conclusions: The study found that the first year of the treatment was the most beneficial for the patients'height growth, with the GH treatment not resulting in any major side effects.

P3-d3-1308 GH and IGF Physiology and Treatment 9

Growth hormone treatment in children with cystic fibrosis born small for gestational age

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Background: Many authors have treated cystic fibrosis (CF) children with recombinant human growth hormone (rhGH) with satisfactory results on the growth, respiratory function and nutrition. Otherwise, small for gestational age (SGA) children, is an accepted indication for rhGH treatment.
Objective and hypotheses: We treated four prepubertal CF children, age < 13 years with rhGH in a dose of 0,3 mg/kg/week.
Methods: They were all followed up by a three month evaluation visit, when weight, height and glucose tolerance were measured. Pulmonary function was assessed at six month intervals.
Results: At the start of therapy, mean height standard deviation score (SDS), was -2,1 ± 0,34. Mean body mass index (BMI) was 16,6 ± 1,2. None of the children had glucose intolerance. Pulmonary function expressed by Forced vital capacity (FVC) predictive was 99,5 ± 0,5% and Forced Expiratory Volume in one second predictive (FEV1)was 106,6 ± 35%. After 12 months, mean height SDS increased to 0,7 ± 0,3 and mean BMI increased to 17,8 ± 0,5. FVC remained 98,1 ± 0,3 % predictive and FEV1 was 104,3 ± 0,7%. The subjects did not develop glucose intolerance nor had any hospitalisations.
Conclusions: Our experience in the treatment with rhGH in CF children born SGA was positive with improvement of growth and nutrition. All children had a good pulmonary function at the start and at the end of treatment.

P3-d3-1309 GH and IGF Physiology and Treatment 9

Multiple dose trial of long-acting growth hormone (NNC0195-0092) in Japanese and non-Asian healthy subjects

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Background: Human Growth Hormone (hGH) is usual administered as a daily subcutaneous injection. NNC0195-0092 is a novel hGH derivative, consisting of a single point mutation in the hGH back bone to which a non-covalent albumin binding moiety has been attached., developed with the aim of reducing clearance and thereby prolonging the exposure leading to once weekly subcutaneous administration.
Objective and hypotheses: To determine safety, tolerability, PK, IGF-I and IGFBP-3 of single and multiple subcutaneous (s.c.) doses of NNC0195-0092 in healthy male subjects compared to placebo.
Method: In this trial, the pharmacokinetics, pharmacodynamic, safety and tolerability parameters of multiple subcutaneous administration of NNC0195-0092 in healthy male subjects (equal numbers of Japanese and non-Asian subjects) were evaluated. Four cohorts of 16 subjects were dosed with multiple subcutaneous weekly administration of NNC0195-0092 (n=12) or placebo (n=4). The doses were escalated between the cohorts in a sequential mode. Blood samples for assessment of pharmacokinetics and pharmacodynamic response (Insulin-like Growth Factor-I (IGF-I), IGF Binding Protein-3 (IGFBP-3)) were taken up to 168 hours after dosing.
Results: Four cohorts were dosed with NNC0195-0092 doses ranging from 0.02 - 0.24 mg/kg. Pharmacokinetic, pharmacodynamic, safety and tolerability data will be presented.
Conclusions: Will be presented at ESPE

P3-d3-1310 GH and IGF Physiology and Treatment 9

Divergent response to growth hormone therapy in 2 siblings with *SHOX* haploinsufficiency

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Introduction: *SHOX* haploinsufficiency is characterized by disproportionate short stature with shortening of the mesomelic limb segments and Madelung deformity. Studies with recombinant human growth hormone (rhGH) showed a height velocity (HV) acceleration in patients with *SHOX* haploinsufficiency and height gains with respect to final height (FH) in response to rhGH treatment similar to patients with Turner syndrome.
Case-reports: We here report 2 siblings with disproportionate short stature due to *SHOX* haploinsufficiency, caused by a not yet reported missense mutation c.503G>A (p.Arg168Gln) in exon 4 of the *SHOX* gene. rhGH (Humatrope®, Eli Lilly, 50 µg/kg/day) was started in the boy at the age of 10.9 yrs (Greulich & Pyle bone age: 11.0 yrs) with a height of 129.5 cm (- 2.5 SDS), and in his sister at the age of 9.6 yrs (bone age: 9.5 yrs) with a height of 126.3 cm (- 1.8 SDS). The boy was prepubertal (A1P1G1) whereas the girl was in early puberty (A1P1M2). During the first year of treatment HV increased from 3.4 cm/yr to 8.7 cm/yr in the boy, and from 3.8 cm/yr to 9.1 cm/yr in the girl, and H-SDS increased to - 1.8 SDS and - 1.2 SDS, respectively. The boy had a good pubertal growth spurt and reached a final height of 163.0 cm (- 2.0 SDS) after 4 ½ yrs of rhGH treatment, resulting in a height gain of +0.5 SDS. The girl, however, progressed rapidly during puberty with an accelerated bone maturation, and growth stopped at the age of 13.4 yrs at a height of 144.8 cm (- 2.3 SDS), resulting in a height loss of 0.5 SDS.
Conclusion: Treatment with rhGH results in a good acceleration of HV in patients with *SHOX*-haploinsufficiency. As it has been suggested that in these patients the pubertal growth spurt is attenuated due to the early closure of the growth plates, the addition of gonatropin-releasing hormone analogs to the rhGH treatment during early puberty seems to be warranted in order the obtain a relevant increase in final height.

P3-d3-1311 GH and IGF Physiology and Treatment 9

Effect of GH treatment on height velocity of children with pycnodystosis

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Background: Pycnodysostosis is a rare autosomal recessive osteochondrodysplasia resulting from osteoclast dysfunction. Growth hormone (GH) secretion impairment and low Insulin growth factor1 (IGF-I) concentrations were reported in these patients.
Objective and hypotheses: The present study aims to describe GH effect on linear growth of eight children with Pycnodysostosis.
Methods: This study was conducted on 8 children suffering from pycnodysostosis. After evaluating systemic diseases, adrenal insufficiency, and hypothyroidism, bone age, height standard deviation score (HtSDS), body mass index (BMI), and some demographical characteristics were measured. To measure the serum GH, clonidine test was performed twice. With initiation of the trial, human GH was injected subcutaneously once a day 6 days a week for a period of 1.5 years (50ug/kg/day). The patients were followed up every 3 months to document their height and BMI until 6 months after the end of the treatment.
Results: All of the patients had growth hormone deficiency**.** HtSDS at the first visit continued to decrease during the 6months before starting the treatment; however, HtSDS started to increase after beginning of GH administration. This value again declined after discontinuing the GH therapy. Overall, the mean of linear growth was improved after GH consumption in the patients.
Conclusions: The present clinical study revealed that GH administration had a positive impact on the linear growth of the children suffering from pycnodysostosis.

P3-d3-1312 GH and IGF Physiology and Treatment 9

Morphological findings of pituitary in patients with growth hormone deficiency (GHD) and correlation with height standard deviation score (HSDS) before treatment, 6 months and 12 months after treatment

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Background: Morphological abnormalities in pituitary can be a cause of GHD.Pituitary tomography (PT) and pituitary magnetic resonance (MRI) are the methods that identify abnormalities in pituitary and may indicate the severity of hypopituitarism.
Objective: Identify morphological findings of pituitary in patients with GHD and associate HSDS before treatment (HSDS-BT), 6m and 12 months after treatment in patients with and without abnormalities.
Methods: Was performed survey of reports of MRI and / or PT of patients with pituitary GHD since 1993 until 2012 at the same service. Analyzed: sex, chronological age (CA) at beginning of treatment; HSDS-BT, 6 months and 12 months after treatment and, HSDS-target height (HSDS-TH). Was compared HSDS of the patients with and without abnormalities in pituitary at these times. Ethical approval was obtained.
Results: 99 patients were studied, 57 male. Medium CA at the beginning of the treatment was 10.4y (3.5-15.7). In 26 patients were found 34 morphological abnormalities at pituitary, highest prevalence of hypoplasia. Patients who had pituitary abnormalities had the HSDS significantly below than who hadn't abnormalities, at diagnosis (-2.54 vs -1.77; $p< 0.05$), 6 months (-2.2 vs -1.35; $p< 0.05$) and 12months (-1.78 vs -1.2; $p< 0.05$) after the beginning of the treatment respectively. In patients with and without abnormalities there were significant difference between HSDS-BT, 6m and 12m when compared with HSDS-TH. There was progressive improvement in HSDS when compared with HSDS-TH. At 12 month, HSDS in girls without abnormalities didn't present more difference with HSDS-TH ($p=0.24$).
Conclusions: HSDS in patients with pituitary abnormalities were worse than without pituitary abnormalities. A longer treatment time is a relevant factor for recovery of height on these patients. After one year of treatment, girls without pituitary abnormalities, have HSDS similar to HSDS-TH, puberty could accelerate growth at this time.

P3-d3-1313 GH and IGF Physiology and Treatment 9

Pediatric patients diagnosed with small for gestational age (SGA), growth hormone deficiency (GHD), and idiopathic short stature (ISS) fulfilling birth weight criteria for SGA status: results from the ANSWER program®

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Background: The ANSWER Program® is a non-interventional study established in 2002 in patients treated with Norditropin® (somatropin) in a real-world practice setting.
Objective and hypotheses: To assess the proportion of SGA, GHD and ISS pediatric patients enrolled in the ANSWER Program who fulfill birth weight (BW) criteria defining SGA potentially used prior to and after the 2007 SGA consensus statement.
Methods: 6079 patients with GHD, SGA or ISS were included. BW standard deviation score (BWSDS) was calculated based on sex, BW and gestational age using the Usher-McLean method. Three separate cutoff values were used to define SGA: BWSDS≤ -2.0 (= lowest 2.3%), ≤ -1.88 (3%) and ≤ -1.65 (5%). The SGA consensus criteria adopted in 2007 are BW and/or birth length (BL) ≤ -2 SDS; this analysis focuses only on BW.
Results: SGA patients were the youngest (age in years: 8.5 for SGA, 10.6 for GHD, 11.2 for ISS) and shortest (height SDS: -2.5 for SGA, -2.1 for GHD,

-2.2 for ISS) among the 3 groups at time of enrollment. Mean BWSDS: -2.2 for SGA; -0.2 for GHD; -0.5 for ISS. BWSDS≤ -2.0 was present in 65% of patients in the SGA group, 6% in the GHD group and 7% in the ISS group. Proportions of patients in the SGA group fulfilling the two less strict criteria was 68% and 72% when BWSDS≤ -1.88 and BWSDS≤ -1.65 criteria were used respectively.
Conclusions: 65% of patients diagnosed with SGA by their physicians fulfilled the strict BW criterion for SGA as defined by the SGA Consensus Statement, while 72% met the least rigorous criterion used in this analysis. It is possible that BL was also used to define SGA in some patients. 6% of GHD and 7% of ISS patients could be defined as SGA by BWSDS ≤ -2.00, which highlights potential ambiguities between these diagnoses. These results uncover an educational need to inform physicians of the consensus definition of SGA. Proper recognition of SGA will also differentiate between diagnoses and may help optimize GH treatment regimens.

P3-d3-1314 GH and IGF Physiology and Treatment 9

Switching to Omnitrope® from other recombinant human growth hormone therapies: a retrospective study in an integrated healthcare system

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Background: Patients switch rhGHs as they move from one health care provider to another and as they change from one pharmacy benefit plan to another. Though there are many pre-FDA approval studies demonstrating the effect of changing from one rhGH to another there is limited retrospective data published demonstrating the effect of patients switching from other rhGH therapies to Omnitrope® in an integrated US healthcare system.
Objective and hypotheses: This study evaluated, through auxologic measurements, the effect of switching children younger than 18 years of age with GHD to Omnitrope® from a non-Omnitrope® rhGH. Additionally, the effectiveness of Omnitrope® on children younger than 18 years of age with alternative short stature diagnoses such as Turner syndrome (TS) or idiopathic short stature (ISS) were explored.
Methods: This was a retrospective pre-/post-switch study from June 1, 2007 to October 31, 2011. Patients included in this study were younger than 18 years of age during the time of their switch to Omnitrope®, were on a non-Omnitrope® rhGH for at least 21 months prior to switching and were evaluable, while taking Omnitrope® for at least 9 months. The patients had diagnoses of GHD, ISS and TS. Quantitative outcomes such as height, HSDS, height velocity and HVSDS were calculated during the 9 months pre-switch and for the 9 months post-switch.
Results: A total of 103 patients were identified (GHD=57, ISS=26 and TS=20). The mean age was 11.29 ± 3.34 years, 54% were female, 23 patients were pubertal and 80 patients were pre-pubertal. The mean heights for patients with GHD, ISS and TS at the time of switching were 137.29±21.4 cm, 144.99±14.71 cm, 129.23±10.78 cm respectively. Subsequent changes in auxologic parameters were consistent with expected norms.
Conclusions: Patients diagnosed with GHD, ISS and TS can switch from a non-Omnitrope® rhGH therapy to Omnitrope® without negatively impacting auxologic parameters.

P3-d3-1315 GH and IGF Physiology and Treatment 9

Efficacy and safety of recombinant human growth hormone therapy for 155 children with short stature

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Objective and hypotheses: To explore the efficacy and safety of recombinant human growth hormone (rhGH) for improving the growth of children with short stature for 12 months.
Methods: 155 children with short stature who accepted rhGH therapy in Fuzhou Children's Hospital of Fujian were analyzed retrospectively, the children were 9.61±3.26 years old. Among them, 107 had growth hormone deficiency, 17 with idiopathic short stature, 21 with Turner syndrome, 10 with small for gestational age, the doses of rhGH were 0.1IU/kg·d~0.15IU/kg·d, Height velocity and increment in height SDS (HtSDS) were studied. Serum IGF-1, TSH, FT4, insulin, blood glucose and blood lipid was examined every three months.
Results: After 12 months rhGH therapy, the growth velocity increased to (8.98±2.77) cm/year, HtSDS were -2.93±1.48, -2.46±1.33, -2.19±1.3 before and after the 6 months and 12 months therapy respectively ($P< 0.05$). After one month rhGH therapy, IGF-1 increased from (173.04±119.31) ng/ml to (304.29±148.41) ng/ml ($P< 0.05$), and afterward, IGF-1 kept stable during the follow-up. In the period of therapy, FT4 had the transient descent in two patients, but TSH hadn't change. There weren't different in glucose metabolism and lipid metabolism before and after the therapy ($P >0.05$). Aminopherases had the transient abnormal in three patients. Five patients were found thickening in injection sites where ultrasound showed fatty tissue. 86 patients took the spinal X-ray, light scoliolosis were found in 20 patients before the therapy, slight aggrevated scoliolosis was found in the patient with Turner syndrome after one year therapy.
Conclusions: rhGH therapy for short stature children can improve the growth velocity and has certain efficiency. The overall safety profile of rhGH continues to be favorable, but careful monitoring for the presence of certain conditions is important both during and after therapy. Children with Turner syndrome are at risk for scoliolosis, which should be regular follow-up.

P3-d3-1316 GH and IGF Physiology and Treatment 9

System construction for quality assurance, quality assessment and quality control of clinical medical examination process of SS (short stature) with GHRT (growth hormone replacement therapy) using the PCAPS (patient condition adaptive path system) and EMR (electrical medical record)

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Background: It is needed sharing clinical medical examination process of SS with not only medical profession but people who are teachers, public officials or so on. In order to share its concept, it is necessary to visualize structure and standardize clinical medical examination process.
Objective and hypotheses: In this study, clinical path of GHRT using Excel to standardize the medical records was implemented to the EMR system. Next, we implemented current clinical pathway analysis and identified problems of the clinical medical examination process of SS using PCAPS.
Methods:
(1) We implemented the electronic information about "GHRT path" created in Microsoft Excel ® to the operational system of Fujitsu. When our team examined a patient with GHRT and described the usual medical record, we carried the "GHRT path" out and typed the requirements in it. We performed periodic verification in a team and then extracted problems.
(2) We created a "SS content of PCAPS" as a clinical practice process hav-

ing adapted for SS patients' state in reference to the clinical practice guidelines and clinical practice. We mounted "SS content of PCAPS" on PCAPS-Administrator. We typed the data in the PCAPS-Administrator. Then we analyzed the clinical pathway converted to process data.
Results: We were able to identify clinical pathway of a comprehensive team medicine for children in need of GHRT. We were able to help their parents to understand the situation by providing a clinical process to visualize growth record of SS patients. It became clear agendas to manage patients with SS by analyzing the data of them as clinical pathway through the use of PCAPS.
Conclusions: "SS content of PCAPS" made focus attention on the data needed for analysis of clinical pathway. "SS content of PCAPS" was designed to standardizing medical process, so it makes clear the difference between a clinical pathway of patients and one of standard and it can help identify individual issues.

P3-d3-1317 GH and IGF Physiology and Treatment 9

Growth hormone treatment in short stature children born small for gestational age

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Background: Most children born small for gestational age (SGA) show catch-up growth, generally defined as growth velocity (GV) greater than the median for chronologic age and gender, within the first 2 years of life; approximately 10% fail to show catch-up growth and may remain short-statured as adults. Growth hormone (GH) therapy has been approved for long-term therapy of growth failure in short-statured children born SGA who show no evidence of catch-up growth by age 2 to 4 years. The objectives of GH therapy in short SGA children are catch-up growth in early childhood, maintenance of normal growth in childhood, and achievement of normal adult height.
Objective and hypotheses: We report the auxological data of six SGA children treated with GH for 2 years.
Methods: 3 males and 3 females with a median birth weight of 685 g (range 520-2290) < 3° centile (ct) according to Gagliardi references were evaluated. Median chronological age (CA) at baseline was 5.2 yrs (range 4.0-9.3); median height was 98.7 cm (range 93-121) < 3° ct according to SIEDP Italian Growth Curves. Median target height was at 25° ct (range 10°-50°).
Results: After 1 year of GH treatment median height was 108 cm (range 101-129); after 2 years median height was 112.5 cm (range 105.5-136), with a median GV of 8.8 cm/yr during the first year (range 8-10) and a median GV of 5.8 cm during the second year (range 3.5-9). Median CA at last clinical evaluation was 7.5 years (range 6.5-11.3). Median IGF-I levels at baseline were 104.5 ng/ml (range 104-109); after 2 years of GH treatment median IGF-I levels remained unchanged at 104 ng/ml (range 98,3-110) and no significant increase of fasting blood glucose levels was observed.
Conclusions: Our data confirm that there is an important variation in the growth response of SGA children to GH treatment, indicating that SGA represents a heterogeneous condition in which response during the first year is the most important predictor of subsequent growth response.

P3-d3-1318 GH and IGF Physiology and Treatment 9

Comparison of growth patterns between patients with congenital MPHD and those due to an abnormal delivery

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Background: Mostly no differentiation is made between patients with MPHD of different etiologies.
Aim: To compare the perinatal and post-natal growth in 2 groups of patients with MPHD including GH.
Subjects: Forth five patients (27m, 18.f): were treated and followed until late adult age. 20 patients were of consanguineous families. According to etiology they were divided into 2 groups: Gr I congenital MPHD (155m, 17f) and Gr II MPHD due to abnormal delivery (12m. 1f).
Results: Thyroid hormones were started in infancy in 27 patients. Age at referral of Gr II patents was younger than that of Gr I abnormal delivery drawing early attention. 9 patients started hGH below age 6, and 6 below age 10. The table shows the main results.

Group Sex, n	At birth Wt (kg)	At birth Lgth (cm)	Start of hGH HC (cm)	Start of hGH Ht (cm)	GH+sex hormones Rx yrs	GH+sex hormones GV (cm/y)	Final Ht (cm)	Final HC (cm)	Present Age yrs
GI m 15	3.4 ±0.6	49 ±2.7	49.9 ±46	103.3 ±27.7	10.8 ±5.7	5.98 ±1.2	159.0 ±14	55.49 ±2.3	49.4 ±20.9
GI f 17	3.0 ±5.15	47.6 ±0.6	50.4 ±1.6	113.5 ±19.3	6.8 ±2.9	5.3 ±1.6	150 ±9.6	54.2 ±2	51 ±13.2
GII m 12	2.63 ±0.6	47.5 ±3.8	51.9 ±1.7	119.7 ±19	8.6 ±3.7	5.1 ±1.7	163.6 ±5.6	54.9 ±1.1	43 ±11
GII f 1	2.1		48	116	5	4.5	138.6	49	25.5

[Table 1]

As m±SD. HC=head circumference, Ht=height, GV=growth velocity, Lgth=length
Conclusions: The mean birth weight of the males in Gr I was higher than in Gr II (P< 0.009). The mean birth length of all neonates was greater than that of neonates with cong IGHD/IGFI def. but lower than of healthy newborns. Education of the public reduced age at referral and enabled earlier treatment in the last decades.

P3-d3-1319 GH and IGF Physiology and Treatment 9

Clinical features and vitamin D levels in paediatric patients with growth hormone deficiency

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Background: Growth hormone (GH) defitienty is diagnosed in children of various age. Vitamin D (D vit) as important factor for bone calcification is beeing suplemented during first two years of life. Lack of D vit is important for all persons, especially in growth hormone defitient children during substitution therapy.
Objective: To evaluate clinical features and D vit level in pediatric GH hormone defitient patients who are treated with GH.
Methods: Patients with GH defitienty are evaluated according their clinical features: sex, age, age at start of GH suplementation, bone age delay at start of therapy, other hormones defitienties, dose of GH suplementation, vit D3 level.
Results: We analyzed 59 patients (31 M/28F), mean age 14.2 y (5-18), mean age 12.1(5-17)y at GH treatment start, and bone age -3 SD (-1SD to -5 SD) compared with chronological age. 15 patients (25%) had hypothyreosis treatment, before diagnosing GH defitienty and in the first year of treatment we started L-thyroxin in 10 (17%) patients. Our patients used Norditropin Nordilet of 10 mg/1,5ml, subcutaeous application once daily in the evening, with mean dose 0.13 IU or 43 mg/kg/ daily. Mean level of D vit in all patients was 19.7 ng/ml (ref. ≥ 40.0) range from 8.0 to 45.6 ng/ml.
Conclusions: Diagnosis of GH defitienty was set up relatively late in our patients. Because of frequency of other defitientes it is necessary to evaluate thyreoid hormone status and vitamin D level and give suplementation if it is necessary. That will probably be of great help for final treatment outcome of this long-lasting demandable treatment.

P3-d1-1320 Glucose Metabolism 15

Extra-hepatic portal vein obstruction and type 1 diabetes in a child: a co-incidence or causal association?

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Background: We report an eight year old boy who had extra hepatic portal vein obstruction (EHPVO) and developed type1 diabetes (type1 DM).This is only the fourth case reported in literature, to have EHPVO who developed type1 DM.
Case report: An eight year old boy presented with polyuria and polydipsia for 1 month. On examination, spleen was enlarged (6cm) without hepatomegaly. There was no history of abdominal infections like peritonitis, pan-

creatitis and umbilical sepsis or umbilical artery catheterization in neonatal period. Blood sugar was 460 mg/dl. Ultrasonography showed portal vein cavernoma and splenomegaly. Endoscopy revealed grade 2 esophageal varices. Thus diagnosis of EHPVO with portal hypertension and type1 DM was confirmed. Other investigations including liver functions, hemogram, renal functions, serum amylase, lipid profile, thyroid function, serum Protein C, S and factor V Laiden were normal. C-peptide level was low (0.111 ng/ml) with weakly positive Islet cell antibodies, positive GAD 65 antibodies (> 2000 IU/ml). Tissue peroxidase and Tissue transglutaminase antibodies were negative. Patient is asymptomatic after endoscopic band ligation of esophageal varices and split-mix insulin regimen.

Discussion: In the index case sequence of events seems to be portal vein thrombosis, leading to cavernoma formation, narrowing of portal vein and asymptomatic portal hypertension over years. Similar sequence was seen in two previously reported patients of EHPVO who developed type1 diabetes. Only condition which can cause both EHPVO and type1 diabetes is pancreatitis. However, there is no proof of pancreatitis in the index case. Authors in above report of 3 cases have also suggested that any disease in portal vein may incite inflammatory response in the pancreas.

Conclusions: In the index case it looks more of a co-incidence rather than a causal association between the two entities.

P3-d1-1321 Glucose Metabolism 15

Helicobacter pylori infection and metabolic control in young type 1 diabetes mellitus patients

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Background: Diabetic patients with poor metabolic control have significantly more long-term complications of the disease such as nephropathy, neuropathy and retinopathy. Infections can elevate the blood glucose levels in patients with diabetes. *Helicobacter pylori* (HP) is one of the most worldwide common chronic bacterial infections. There is no consensus in literature whether HP infection is associated with impaired metabolic control in diabetes mellitus patients.

Objective and hypotheses: To evaluate the association between HP infection and metabolic control in young type 1 diabetes mellitus (DM1) patients.

Methods: We studied prospectively young DM1 patients followed-up at the same institution (Hospital das Clínicas da Universidade Federal de Minas Gerais - UFMG), whose glycemia, HbA_{1c} levels and required doses of insulin could be affected by HP infection. We excluded patients with diabetes long-term complications, and autoimmune or disabsorptive intestinal diseases. HP infection was diagnosed by using the ^{13}C-urea breath test (^{13}C-UBT). Metabolic control was evaluated by HbA_{1c} levels (HPLC method, RV according to ADA criteria) and insulin doses (UI/kg/day) in infected patients and their uninfected counterparts. Data were evaluated using SPSS software. A P value < 0.05 was considered statistically significant.

Results: We studied 119 patients (54 males, 65 females), 2 to 20 years old, (median: 13.7). The prevalence of HP infection was 29,4%. HP-infected diabetic (n = 35) were older than non-infected patients (n = 84): 15.8 ys *versus* 13.2 ys; p= 0.03. There was no difference in the HbA_{1c} levels between infected and non infected patients (OR: 0.55; CI: 0.19-1.58; p = 0.27). The insulin requirement (total, basal or bolus doses) for both groups was similar (p value = 0.12; 0.42; 0.14, respectively).

Conclusions: This group of young type 1 diabetic patients infected with HP did not present impaired parameters of metabolic control compared to the non-infected one.

P3-d1-1322 Glucose Metabolism 15

Warts of the fingertips in a paediatric diabetic patient

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Case presentation: An 11-year old girl with type 1 diabetes mellitus presented to the pediatric endocrinology clinic for her scheduled quarterly follow up. Her diabetic control was suboptimal, with a hemoglobin A1c of 11.4%.

During her visit, her mother reported that during the past few months, she had started developing painless, dark lesions on her fingertips. These lesions were appearing in the same areas that she used to prick her skin with a lancet, for her capillary blood glucose monitoring.

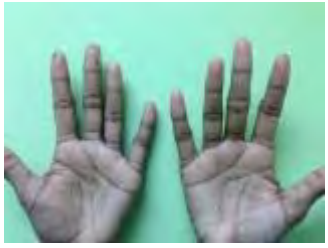
On physical examination she was found to have multiple hyperkeratotic, hyperpigmented lesions of different sizes, that fit the clinical diagnosis of common warts. (Figure 1). Common warts are the result of a cutaneous HPV (human papillomavirus) infection.

On further questioning, the girl revealed that she rarely changed the lancet from her lancing device, and that she had been reusing the same lancet for periods of weeks at a time.

Reusing of the same lancet resulted in subsequent inoculation of her fingertips with HPV.

Both the patient and her mother were advised not to reuse the lancets and the patient was referred to dermatology for treatment of her warts.

We found another report of a similar case in an adult patient with type 2 diabetes mellitus in the literature.



[Figure 1]

P3-d1-1323 Glucose Metabolism 15

Frequency of skin alterations in children and adolescents with type 1 diabetes and insulin pump treatment

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Background: Subcutaneous insulin infusion via insulin pump is common in children and adolescents with type 1 diabetes. The insertion of catheters is performed in the abdomen, gluteal region, legs or arms.

Objective and hypotheses: The local fixation of catheters on the skin is performed with plasters and the needle or teflon catheters stay inserted for at least 48 hours. We hypothesize, that longer insertion time and plaster fixation may cause skin irritations.

Methods: In a single centre setting 65 patients with insulin pump treatment were asked to take part in a clinical observation with photo-documentation of the catheter insertion side and to answer a questionnaire . 54 (83%) of patients (26 female, 28 male) aged 3 to 20 years took part in the observational survey. A questionnaire about diabetes duration, duration of pump treatment, pump model, catheter-model, types of insulin used, insertion time and handling were analyzed.

Results: 44,4% (9 female, 15 male) of patients showed local disturbances of the skin. Scars were observed most often (54,2%, 6 female, 7 male), followed by lipo-hypertrophy (45.8%, 4 female, 7 male) and eczema (25%, 1 female, 5 male). Furthermore hyper pigmentation (12.5%, 1 female, 2 male) and lipoatrophy (12.5%, 1 female, 2 male) were seen. Two female patients (8.2%) showed subcutaneous infections with surgical treatment needed. 54.2% (6 female, 7 male) needed to switch the insertion region, a switch from pump treatment to injections via syringe or pen due to skin alterations could not be observed.

Conclusions: In our observation, skin alterations were frequently occuring side effects of insulin pump treatment in children and adolescents. The relative high frequency of lipo-atrophy is interesting and needs further investigation in a multicentre setting to clarify, if there is a real association with insulin pump treatment.

P3-d1-1324 Glucose Metabolism 15

Permanent neonatal diabetes mellitus due to insulin gene mutation in northeast of Thailand: case report

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Introduction: Neonatal Diabetes Mellitus is a rare disease which characterized hyperglycemia before age of 6 months. This disease divided in 2 main group, Transient NDM and Permanent NDM by duration of insulin dependent in early period of life. Transient NDM occurs about 50-60% 0f cases NDM and resolved withtin few months. Clinical presentation can not predict the prognosis whether transient or permanent NDM. So molecular diagnosis which involve pancreatic synthesis,function and insulin synthesis should be done. Some forms of NDM may change treatment from insulin injection to sulfonylurea administration.
Case study: The author report 1 male infant diagnosed NDM at age 9 weeks. He presented with pneumonia, respiratory failure, hyperglycemia and DKA. After clinical improved, glucometer persisted 200 - 500 mg/dL before meal. Ultasound abdomen was normal. The molecular diagnosis was done. The result was heterozygous mutation of INS gene, missense mutation p.F48C. The result confirm diagnosis of permanent NDM. His treatment were intermediate acting insulin (insulatard®) and rapid acting insulin(novorapid ®). After treatment, he had normalized growth and development.
Conclusion: NDM is a rare disease, which should be differentiated from other conditions that presented with hyperglycemia in infants. Molecular study about pancreatic function, pancreatic synthesis and insulin are usful for diagnosis and prognosis of disease. Some forms of NDM may change treatment from insulin injection to sulfonylurea administration.

P3-d1-1325 Glucose Metabolism 15

Clinical and genetic characteristics of diabetes mellitus in adolescents in Siberia

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Background: The prevalence of diabetes mellitus in the world-wide increase in the epidemic, as well an increasing number of young patients (debut of diabetes up to 18 years).
Objective and hypotheses: We studied the City Register of diabetes in Novosibirsk. 1242 patients had disease onset before 18 years. 409 patients (371 - with type 1 and 38- with type 2) had a family history of diabetes, 70 of them (34 with type 1 diabetes, 36 - type 2) were invited in examination.
Methods: We did these patients clinical examination, biochemical, hormonal (C-peptide) analysis, determination of antibodies to b-cells. We researched the clinical and laboratory findings in these patients and formed a group with unusual characteristics for previously diagnosed type of diabetes. 22 patients were included in this group: 20 people had been previously diagnosed with type 2, 2- type 1, we performed them molecular genetic testing for the presence of mutations of glucokinase (MODY 2 diabetes).
Results: 5 patients of 22 (4 primary had a diagnosis 2 type of diabetes, 1 - 1 type) had MODY 2. 3 people have a mutation in exon 7, 1- in 4exon, 1 - 1 exon glucokinase. The mean age at onset of the disease was 12,6 ± 4,3 years. 3 people (60%) had no symptoms at the onset and the diagnosis of diabetes is exposed to laboratory data. All patients had a normal body weight. 1 patient using insulin therapy, 2 - diet therapy,2 - oral hypoglycemic drugs. Mean level of C-peptide was 0,30 ± 0,21 ng / mL (reference values 0,7-1,9).
Conclusions:
1. Half of the patients with 2 type diabetes and with the debut up to 18 years had family history of diabetes.
2. Adolescent with 2 type diabetes, normal body weight and asymptomatic debut should be a thorough differential diagnosis of diabetes type using molecular genetic testing.

P3-d1-1326 Glucose Metabolism 15

Paradoxical hypoglycaemia associated with the use of high dose diazoxide for the treatment of hyperinsulinaemic hypoglycaemia

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Background/aims: Hyperinsulinaemic Hypoglycaemia (HH) is the most common cause of severe and persistent hypoglycemia in the neonatal period. Diazoxide, a K_{ATP} channel activator, is the first line of treatment for patients with HH.
Methods: We present two cases diagnosed with HH in the neonatal period. Both were started on diazoxide as the first line of treatment and the dose was titrated in order to achieve euglycemia.
Results: When the dose of diazoxide was increased to 15mg/kg/day, we noted that both infants had multiple episodes of hypoglycemia. The episodes resolved as soon as the diazoxide was stopped. The period between the increase in the dose of diazoxide and the onset of hypoglycemia varied from 12-48 hours.
Conclusion: We report for the first time that diazoxide can cause paradoxical hypoglycemia when used in high doses in infants with HH.

P3-d1-1327 Glucose Metabolism 15

Evaluation of DCA Vantage for rapid in-clinic measurement of HbA1c on capillary blood in young patients with type 1 diabetes

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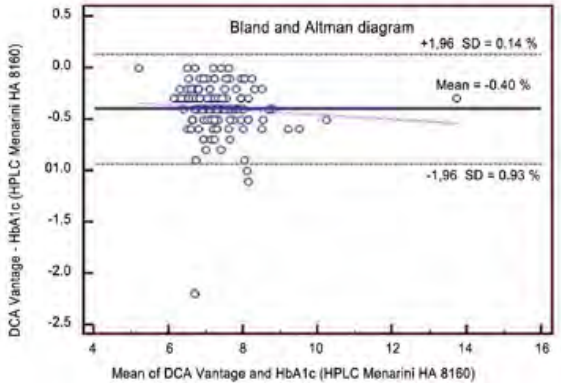
Background: HbA_{1c} is a gold standard measure of overall diabetes control, and HbA_{1c} values serve as the targets for diabetes management. Rapid in clinic measurement of glycated hemoglogine HbA_{1c} allows to determine the level of metabolic control within a few minutes on capillary blood.
Objective and hypotheses: Compare the results of measurement of HbA1c with DCA Vantage (Bayer, Inc.) based on an immunological technique with a reference method by HPLC (High Pressure Liquid Chromatography) in young type 1 diabetic patients.
Patients and methods: The study included 120 unselected young type 1 diabetic patients, with different degrees of metabolic control. All patients makes at least 4 glycemic control per day. We use the DCA Vantage at the same time as the sample for HPLC system is taken. The DCA Vantage was compared with the HPLC system (Menarini HA 8160) whose deviation from the DCCT was < 0.1 % across the clinical range. Statistically we used approach of bland and altman.



[Figure 1]

Results: The mean underestimation of the DCA Vantage was -0.40 %. The agreement limits (±1.96 SD) were between 0. 14 % and - 0.93 %; this means ± 0.53 % around -0.40 % (Figure1).
Conclusions: The DCA Vantage underestimates HbA_{1c} levels; however it met the acceptance criteria of having a coefficient of variation < 3 %.

P3-d1-1328 Glucose Metabolism 15

Hyperinsulinaemic hypoglycaemia associated with a novel mutation in the SCHAD gene

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Introduction: Hyperinsulinemic hypoglycemia due to short chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency is one of the rarest abnormalities in pancreatic β-cell insulin regulation.
Case study: The patient was born to a G1P1 healthy mother at 38 weeks gestation via cesarian section for failure to progress. Birth weight was 3,7 kgr. Pregnancy was complicated by Gestational Diabetes Mellitus treated with insulin. Parents are consanguineous. He developed severe, refractory hypoglycemia despite aggressive treatment with IV glucose,fluids and oral feeds and laboratory evaluation was concomitantly performed including blood glucose (BG), insulin levels, growth hormone, cortisol, NH3, urine for ketones and screening for Free Fatty Acid (FFA) and organic acid disturbances. Pertinent results: BG: 16 mg/dL, Insulin:21,7 μU/mL, Urine organic acids: elevated 3-hydroxyglutaric acid, Whole Blood organic acid newborn screening (MS/MS) : elevated hydroxy-butyryl carnitine, Molecular analysis of the SCHAD gene: Exon 3 Homozygous G352A mutation, changing glutamic acid to lysine.
The patient was started since then on Diazoxide treatment and has responded well with normalization of the blood glucose. He is currently on regular feeds supplemented by cornstarch before bedtime.
At the age of 2 months he was diagnosed with primary hypothyroidism and was started on thyroxine replacement therapy. He was also diagnosed with unilateral orbital hemangioma partially regressing by triamcinolone/betamethasesone intraocular injections. He exibits mild global developmental delay improving via physical, occupational and speech therapy and will undergo ENT evaluation for possible unilateral sensorineural hearing loss.
Conclusions: Exon 3 homozygous G352A SCHAD mutation is a new mutation leading to Hyperinsulinism. Further studies are needed to identify whether the defect is limited to the pancreatic β-cells or extends to other tissues such as those affected in our patient.

P3-d1-1329 Glucose Metabolism 15

Symptomatic cerebral infarction in a child with severe diabetic ketoacidosis

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Background: Diabetic ketoacidosis (DKA) is a common initial presentation of pediatric Type 1 diabetes mellitus. Cerebrovascular complications of DKA in children are rare condition with a significant mortality and morbidity.
Case report: A previously healthy 4-years-old female patient was referred to our endocrinology department with DKA. Before coming to our center, insulin and bicarbonate boluses had been given to the patient. Laboratory investigations showed ketonuria, acidosis (pH: 6.88, HCO_3:3,5 mmol/L) and hyperglycemia (plasma glucose 492 mg/dL). The patient was then treated with an insulin and sodium bicarbonate and hydrated with intravenous fluids in 48 hours. Despite her altered level of consciousness, there were no signs of cerebral edema. In a few days after admission, her blood sugar was controlled, her mental status was improved and DKA resolved. On the fourth day a left-sided ptosis, right-sided hemiparesis and gait disturbance was observed. Neuroimaging studies including CT scan, MRI and MR-angiography of the brain were performed, showing ischemic/hemorrhagic infarction of left thalamus and mesencephalon. Screening for prothrombotic conditions showed negative results. After 20 days of hospitalization to select the right dose and timing of insulin therapy, she was released in good clinical and neurological recovery.
Conclusion: DKA is a life-threatening condition. Although neurological deterioration in children with DKA is most likely to be as a result of cerebral edema, because of the prothrombotic tendency in these children, clinicians should consider ischemic stroke in the differential diagnosis.We suggest that ischemic stroke of our patient is due to boluses of insulin and bicarbonate that has been given before hydration. Well-defined rehydration strategy in the first hours of therapy is crucial and can reduce neurological complications. For this reason, urgent critical care and diabetes consultation should be obtained.

P3-d1-1330 Glucose Metabolism 15

Glycogen storage disease type 0: case report

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Background: Glycogen storage disease (GSD) type 0 is an extremely rare autosomal recessive disorder that results from mutations in glycogensyntase gene (GYS2). Classical features are fasting ketotic hypoglycemia and postprandial hyperglycemia and hyperlactatemia.
Objective: To identify the structure of GYS2 gene in a patient with complete clinical presentation of GSD type 0.
Clinical case: A 5 yo boy was admitted to our clinic for growth delay (height SDS = -2,71). He had a history of generalized seizures and received valproate since the age of 3 years. There were no evident clinical symptoms of hypoglycemia, however weakness and slight aggression were observed during fasting. Hypoglycemic episodes were stably present in the mornings along with suppressed insulin, c-peptide and postprandial hyperglycemia. On examination there were no dysmorphic features, body composition was proportional, Tanner stage 1, the single remarkable symptom was slight hepatomegaly. The diagnosis of GSD type 0 was suggested. Glucose tolerance and glucagon tests were introduced.
Methods: Direct sequencing of GYS2 gene.
Results:

Glucose tolerance test (Glucose 1.75gr per 1 kg = 24 gr)	0 min	120 min		
Glucose, mmol/l (3.1-6.1)	0.3	6.3		
Lactate, mmol/l (<2.4)	0.7	5.1		
Ketones, mmol/l	3.8	0.4		
Glucagon test (0.03 mg per 1 kg = 0.4 mg)	**0 min**	**5 min**	**10 min**	**15 min**
Glucose, mmol/l (3.1-6.1)	1.9	2.9	2.7	2.7
GH, ng/ml (0.05-6.9)	0.65	IGF-1, ng/ml (27-170)	24.4	
TSH mIU/L (0.6-5.7)	5.3	Free T4, pmol/l (11.5-20.4)	13.9	
Cortisol, nmol/l (77-630)	643.7			

[Clinical data]

Direct sequencing of GYS2 gene revealed a known homozygous mutation in the 7th exone c.1015G>C(Ala339Pro).
Conclusions: Our data underlines the importancy of correct diagnosis if hypoglycemic syndrome, as our patient was initially refered to endocrinologist for growth delay. Remarkable clinical features of this case are growth delay with low IGF-1 level which are described only in a few patients with GSD type 0.

P3-d1-1331 Glucose Metabolism 15

Treatment with growth hormone for one year in a patient with Fanconi-Bickel syndrome with severe short stature

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Background: Fanconi-Bickel syndrome (FBS) is a rare congenital disorder caused by mutations of the gene encoding the glucose transporter protein-2 (GLUT-2), and is characterized by a typical clinical picture, impaired glucose homeostasis (fasting hypoglycemia, postprandial hyperglycemia), galactose intolerance, hepato-nephromegaly and proximal tubular nephropathy with hypophosphatemic rickets and severe failure to thrive. No specific therapy is available but symptomatic treatment usually improves prognosis.
Objective and hypothesis: Treatment with growth hormone might improve height in FBS patients with severe failure to thrive as occurs in inherited hypophosphatemic rickets.
Case report: Our patient was the fourth child of non-consanguineous Dominican parents. He was born by cesarean section with birth weight 2555 g and length 47 cm. Failure to thrive and hepatomegaly was observed at six months of age and diagnostic workup revealed fasting hypoglycemia, postprandial hyperglycemia, hypophosphatemia, hyperphosphaturia, elevated transaminases, glycosuria and metabolic acidosis.Molecular analysis of GLUT-2 revealed an IVS4-2A>G mutation. Treatment included:
1) Diet with frequent feedings during the day and avoidance of fasting, dietary restriction of free glucose and galactose, supplements of cornstarch, high-content fructose and proteins, and nocturnal continuous feeding by gastrostomy.
2) Oral phosphate and vitamin D supplements and
3) oral bicarbonate.
Catch up was not achieved and at 2 years and 6 months of age his weight was -2,85 SD and his height was -6,33 SD. We started treatment with somatotropin (out of label) considering it might be useful as in hypophosphatemic rickets.
Results: After one year of treatment with growth hormone (0,03 mg/kg/day) height increased 1SD.
Conclusions: We present our experience of treating a single case of FBS with somatotropin during a one-year period, but still no specific therapy can be established for this syndrome.

P3-d1-1332 Glucose Metabolism 15

Gut autoimmunity and type 1 diabetes mellitus

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Background: Epidemiological studies convincingly implicate a link between environmental factors and type 1 diabetes mellitus (T1DM). Recent data highlighted the relation of gut micro flora with gut mucosal immunity system and the interaction between autoimmune diseases as T1DM and some of the metabolic diseases.
Objective and hypotheses: Changes in mucosal immunity, aberrant gut microbioma and diminished mucosal layer of intestine have been speculated to involve pathogenesis of T1DM. Actually detection of gut micro flora on mucosal layer would probably be of importance regarding this possible relationship of autoimmune effects of gut.
Methods: We performed our study in newly diagnosed 42 diabetic children (age range: 1 to 16 years, mean age: 7.45 ±3.7 years) and 42 healthy subjects (mean age: 7.45 ± 2) as a control group from September 2010 to February 2011. We compared study group and control group; (1) type of labor, (2) history of feeding type before 1 year of age, (3) presence of celiac disease and (4) culture of stool for fungal organisms.
Results: Type of labor were determined as; 35.7% of cases in study group and 38.9% of cases in control group had sectio. Cow's milk intake before 1 year of age was statistically higher and Celiac disease was diagnosed in two patients in study group. Although it was not statistically significant, we determined antigliadin IgA (+) of 9.5%, antigliadin IgG (+) of 23.8% and antiendomysial antibodies (+) of 7.1% of cases in study group. Notably, Candida albicans detected in stool cultures of 50% of cases in study group as a major flora.
Conclusions: Our results are noteworthy of showing the gut micro flora changes in diabetic patients and may represent a role of gut autoimmunity in pathogenesis of T1DM. Evidence suggests that changes in gut micro flora could not be independent from clinical outcomes and further clinical trials are needed to elucidate its consequences.

P3-d2-1333 Glucose Metabolism 16

A diagnostic conundrum: case of diabetes mellitus and deafness in twin boys associated with unusual associations

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Case report: Male twins, T1 (birth weight 2.2kg) and T2 (2.1kg), born at 37 weeks with subtle facial dysmorphism and bilateral choanal atresia needed surgical correction and at 8 weeks both were treated for pyloric stenosis. By 18 months both twins were diagnosed with sensorineural deafness requiring hearing aid. At 15 years of age both were diagnosed with diabetes mellitus (DM) without ketoacidosis and treated with insulin. Incidentally their mother was diagnosed with Type2 DM and is on oral hypoglycaemics. At presentation T2 was relatively short and prepubertal. On investigations T2 was found to have central hypothyroidism and other investigations (below) were done.

	T1	T2
Height	9th centile	3cm <0.4th centile (Below target centile range)
Pubertal status	Pubertal	Prepubertal
Pancreatic autoantibody negative	Yes	Yes
Adrenal function	9 am cortisol 247nmol/l	Poor response to Synacthen
LHRH stimulation	-	Prepubertal response
Bone age (at age = 16 y)	-	11.7 y
Arginine stimulation test	-	Growth hormone (GH) <0.05 µg/L IGF-1 (<3.3nmol/L) IGFBP-3 (1.5mg/L)
MRI brain	Both had suprasellar lesions suggestive of Rathke's cleft cyst. Larger lesion in T2	

[Clinical and investigations]

T2 was commenced on thyroxine and steroid replacement. Both had normal visual field assessments. Radiological and neurosurgical opinions are to monitor them regularly.
After careful consideration GH was started for T2. Twins were also investigated for Maternally Inherited Diabetes and Deafness (MIDD) and blood for m.3243A>G mutation was negative. T2 currently requires large doses of insulin (2.4 units/Kg/day) while T1 continues to require normal doses (< 1 unit/Kg/day). Twin 2's height velocity has improved on GH. He still remains prepubertal and we are planning to induce his puberty.
Conclusions: We present a complex case, with diagnostic and treatment challenges. There are no similar patients described in the literature. We continue to liaise with geneticist and endocrinologists in search of a unifying diagnosis.

P3-d2-1334 Glucose Metabolism 16

Relationship between metabolic control and neurocognitive functions of children with type 1 diabetes mellitus

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Objective: The aim of our study was to investigate the effects of age at onset of diabetes, glycemic control, duration of disease and treatment methods such as multiple daily injections and insulin infusion pump therapy on neurocogni-

tive functions in children with type 1 diabetes.
Material and method: Twenty two children (8-16 years old) who were diagnosed as type 1 diabetes without comorbidity were included in the study group. Additionally, one control group was recruited from twenty three healthy children. Wechsler Intelligence Scale for Children Revised (WISC-R), Visual Auditory Digit Span Test Form B (VADS-B), Bender - Gestalt Test and Cancellation Test were applied to all children in two groups. Additionally, patients were analyzed in terms of age of disease onset, mean HbA1c levels of recent year, duration of disease and treatment methods.
Results: Neurocognitive functions such as visual motor development, visual spatial memory and visual organisation, visual perception, multimodal short term memory, concentration and continuous attention were seen negatively effected at significant level in type 1 diabetes group. Furthermore, verbal and general intelligence were found to be significantly affected in children with type 1 diabetes who had earlier diagnosis. There was no statistical significance in terms of treatment methods and HbA1c levels.
Conclusion: Negative effects of early onset of diagnosis and prolonged duration of disease on neurocognitive functions were detected in children with type 1 diabetes. We suggest that negative effects of these factors on neurocognitive functions in type 1 diabetes should be considered and evaluated for taking necessary precautions in management of these patients.

P3-d2-1335 Glucose Metabolism 16

Clinical characteristics, genetics and treatment outcome of 6 patients with congenital hyperinsulinism

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Background: Congenital hyperinsulism (CHI) is the most common cause of neonatal, infantile and childhood hypoglycemia. Mutations in 8 different genes has been identified that are responsible for the etiology of CHI.
Objective: To present clinical characteristics, mutation analysis and treatment outcome of 6 patients with the diagnosis of CHI.
Patients and method: 6 patients with the diagnosis of CHI were included. A detectable insulin level (>2 IU/L) in course of hypoglycemia (BG< 50 mg/dl) was considered as diagnostic for hyperinsulinemic hypoglycemia. To confirm the genetic basis of CHI, DNA samples were studied for mutation analysis. Initial therapy for all patients was diazoxide. Octreotide and nifedipine were added as second choice drugs. Cases unresponsive to medical therapy underwent pancreatectomy.
Results: 3 out of the 6 patients were positive for a mutation in the *ABCC8* gene and 1 patient had a mutation in the *HADH* gene. All patients with mutations in *ABCC8* presented at the first week of life. A same frameshift mutation in *ABCC8* gene was detected in two patients, interestingly one with paternally transmitted heterozygous and other with homozygous mutation. However, clinical presentation, treatment response and histological subtype of CHI were very similar. Both patients required pancreatectomy and histologic evaluation of resected pancreatic tissue revealed diffuse form of CHI in both cases. Protein loading test was positive for the patient with the *HADH* mutation.
Conclusions: CHI patients with mutations in *ABCC8* gene can present with severe refractory hyperinsulinemic hypoglycemia in the neonatal period. Despite different transmission pattern two patients with same frameshift (p.L1171fs) mutation in ABCC8 gene had similiar clinical phenotype and histological subtype (diffuse form) of CHI. Mutation in *HADH* gene causes protein sensitive hyperinsulinemic hypoglycemia.

P3-d2-1336 Glucose Metabolism 16

Glibenclamide and repaglinide therapy in two infants with diabetic ketoacidosis and mutation in KCNJ11 gene

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Introduction: Activating mutation of potassium inwardly-rectifying channel J, member 11 (KCNJ11) that encodes Kir6.2 has been associated with permanent neonatal diabetes mellitus (PNDM).
Objective: Here two infants with mutation in this gene are presented who responded to two types of sulfonylurea therapy.
Method: The patients genomic DNA was isolated from peripheral blood leukocytes using the salting-out method [PCR amplification followed by direct sequencing (Genbank NM000525.3)]. Self-monitoring of blood glucose (BG) was done before and 2 hours after milk or foods. IBM SPSS 19 was used for analysis.
Case studies:
Case 1 was a 50 day old girl with poor feeding and fever since 5 days before entry. Physical examination (PE): 10% dehydration, lethargy, weight (W):3.7 kg, height (H):52 Cm. respiratory rate (RR):69/min, temperature (T):39.4°C. Lab. tests: BG, 750 mg/dL; blood pH, 6.88; HCO3, < 3 mEq/L; keton, +2; serum Na, 162 mEq/L; insulin, 0.5 µIU/mL.
Case 2 was a 3.5-month old girl with polyuria, fever and vomiting since10 days before. PE: dehydration, lethargy, RR:45, W:5 kg, H:58 Cm. Lab. Tests: BG, 500 mg/dL; blood pH, 6.98; HCO3, < 3.9 mEq/L; keton,+2; serum Na, 144 mEq/L; insulin, 0.63 µIU/mL. After treatment of ketoacidosis, insulin therapy gradually changed to Glibenclamide (0.4 mg/kg/day divided to 3) in both cases, but due to occurrence of hypo and hyperglycemia in case 2, it was changed to repaglinide (0.046mg/kg/day divided to 8 times, before every milk). Genetic study revealed R201H mutation (Arginine to histidine) in KCNJ11 gene in both of them.
Last visit:
Case 1: age, 23 months; W:13.7 (50% of CDC2000 curves), H:86 Cm (50%), mean ± SD of blood glucose (MBG):129.5 ± 34.5; HbA1C: 3.9%.
Case 2: age, 10 months; W:8 kg, H:69 Cm (both10-25%); MBG:122.59 ± 19.6, HbA1C:4.8%. There was no significant difference between MBG in 2 cases (P>0.05).
Conclusion: Every infant with PNDM may have a genetic mutation that responds to sulfonylurea treatment.

P3-d2-1337 Glucose Metabolism 16

Investigation and analysis of the quality of life in children and youth with type 1 diabetes in China

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Background: The quality of life of type 1 diabetes in China is unknown in recent ten years,we hope to get the message about the current quality of life and the affected factors for better adminsiter diabetes children.
Objective and hypotheses: Investigating the current quality of life in 98 children and youth with type 1 diabetes,evaluating the result in order to find factors that influence the quality of life, in order to establish a suitable scale for Chinese children of type 1 diabetes.
Methods: The American juvenile diabetes patients quality of life scale"Diabetes Quality of Life for Youths" was used to Investigate the quality of life in 98 patients who participated in the Diabetes Summer Camp which held in three cities of Chongqing, Wuhan and Chengdu.While SPSS19.0 was used to analysis the statistics.

Results:
1. The scale has good reliability and validity:whlie the Cronbach's Alpha score is 0.942,the validity score is 0.679;
2. All three areas of the scale have significant Correlations with self-health assessment in 0.01 level;
3. The quality of life in children and youth with type 1 Diabetes was affected:The score of influence area and worry area in these children are higher than the total,the same to the self health assessment score;
4. Course of disease,diabetes diet and blood glucose have positive correlations to all areas in 0.01 level;Age and HbA1c have positive correlations to influence area only;while gender has negative correlation to satisfaction area in 0.05 level.
Conclusions: The quality of life in children and youth with type 1 Diabetes was decreased; especially people who had a longer course of diabetes and female who entered into adolescent, they had a poor diet, and glycemic were poor controlled. So the quality of life was affected.

P3-d2-1338 Glucose Metabolism 16

Two cases of iliopsoas abscess in adolescents with type 1 diabetes mellitus

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Background: Patients with insulin dependent diabetes mellitus (DM) are more susceptible to a range of different infectious complications and in particular to unusual infections. Here we present two cases of iliopsoas abscess, a rare form of retroperitoneal infection, in adolescents affected by type 1 DM.
Case study 1: A 15-year-old girl, with a 9-year history of type 1 DM, presented to our Pediatric Clinic with a 4-day history of progressively worsening right flank pain and fever. Full blood count and biochemistry revealed a severe leukocytosis of 26.6 x 109/l, C-reactive protein of 225 mg/l and marked hyperglycemia with ketoacidosis. Most recent HbA1c was 10%. An ultrasound scan revealed a complex multiloculated right kidney abscess extending to iliopsoas and a computed tomography (CT) scan confirmed the diagnosis. Given the loculated nature of the abscess, it was drained surgically. Staphylococcus aureus was grown from the pus and the patient was successfully treated with appropriate antibiotics.
Case study 2: A 13-year-old girl, with a 2-year history of type 1 DM, presented to our Hospital with the same symptoms. Most recent HbA1c was 7.1% and she had a history of good glycemic control. A computed tomography (CT) scan of abdomen and pelvis showed a left iliopsoas abscess. The infection was treated successfully with antibiotics. Three years later she presented with a recurrent iliopsoas abscess, which was drained surgically
Conclusions: Both our cases demonstrate that type 1 DM is an important factor resulting in primary iliopsoas abscess formation. Case 1 presented in a patient with poor glycemic control while Case 2 presented in a patient with good glycemic control. Our cases suggest that an increased awareness of the iliopsoas abscess diagnosis in adolescents with type 1 DM is required.

P3-d2-1339 Glucose Metabolism 16

A new de novo mutation in the GCK gene causing MODY2

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Introduction: Glucokinase (*GCK*) heterozigous inactivanting mutations are responsible for MODY2, the commonest form of monogenic diabetes in Southern Europe. Clinical characteristics are strict autosomal inheritance, early age of onset of mild persistent hyperglycaemia, glycated haemoglobin level (HbA1c) just above the upper limit, absence of β-cell autoantibodies. *GCK* defects had been rarely reported as "de novo" mutations.
Case report: A 5.5 year old boy was referred to our Centre with mild fasting hyperglycemia (6.56 mmol/l), HbA1c of 6.7% and normal fasting C-peptide level (1.2 ng/mL). Oral glucose tolerance test (OGTT) showed impaired fasting glucose: the 2-hrs glycemia was 6.89 mmol/l, insulin level was 14 μU/ml. BMI was 18.4 Kg/m^2. β-cell autoantibodies were negative. Parents were normoglycaemic and family history was negative for hyperglycemia/gestational diabetes mellitus. At age of 12.3 laboratory data confirmed: persistent fasting hyperglycemia (6.78 mmol/l), HbA1c of 6.5% and absence of β-cell autoantibodies. Based on these clinical parameters even if in absence of family history, genetic testing for MODY2 was performed.
Direct sequencing showed a novel frameshift mutation c.1103_1122_del19nt; p.R368fs27X on *GCK* exon 9. Mutation were absent in both proband's parents.
Moreover, at physical examination, there was evidence of weight gain compared to previous years (BMI=26.6 Kg/m^2). As therapeutic option, only dietary prescription was handed out.
Conclusions: Up to now only 7 "de novo" mutations in MODY2 patients have been reported. It's important to analyze *GCK* in cases with clinical and biochemical features of MODY2, even in the absence of a family history of this disease. Autosomal dominant inheritance as one of the strict diagnostic criteria for genetic testing should be reconsidered.

P3-d2-1340 Glucose Metabolism 16

Continuous glucose monitoring: our experience in 4 patients with documented or suspect metabolic diseases other than diabetes

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Background: Continuous glucose monitoring system (CGMS) is commonly used for detecting hypoglycaemic events in type 1 diabetic patients and for evaluating daily glucose level excursions. In the last years, always more technological CGMS devices has been applicated in the study of other metabolic conditions affecting glucose levels, apart from diabetes.
Aim: To examine the efficacy of CGMS Medtronic in 4 patients with documented diagnosis or suspect metabolic disorders other than type 1 diabetes.
Populations and methods: Among commercially available CGMS, Medtronic System has been used in our Centre in 4 pediatric patients affected by glucose metabolism disorders other than type 1 diabetes: (A) glycogen storage disease Type 1A, (B and C) follow up for suspect hypoglycaemic events correlated with lipotimia, (D) suspect glycogen storage disease Type 0.
Results: In (A) the CGMS was useful for controlling glucose excursions and it determined the importance of small frequent meals and night enteral nutrition in order to avoid serious hypoglicaemic events. In (B) and (C) this device demonstrated that the described lipotimia episodes were not caused by any alteration in carbohydrates metabolism. In (D) the CGMS detected post-prandial hyperglycaemic spikes and recurrent asymptomatic nocturnal hypoglycaemic episodes. We could therefore start a correct prophylaxis for avoiding night hypoglicaemia and we hypotized a glucose metabolism alteration which is not caused by a peculiar deficit.
Conclusions: Experimental preliminary evidences about the use of CGMS in our Centre suggest that this new technology could be applied in diagnosis process and in follow up of patients with suspect or documented carbohydrates metabolic disorders, in order to evaluate full daily glucose excursions, to identify nocturnal hypoglicaemic events (otherwise not revealed by traditional self blood-glucose monitoring) and treat them with the most adequate therapy.

P3-d2-1341 Glucose Metabolism 16

Glycemic variability assessment in association with physical activity performed by children with type 1 diabetes mellitus during summer camp

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Background: Glycemic variability has been identified as a key tool in the evaluation of treatment prognosis in Type 1 mellitus diabetes (T1DM). Growing evidence suggests that the risk of developing micro and macrovascular long-term complications is driven by glucose excursions rather than glycated haemoglobin. High Blood Glucose Index (HBGI) and Low Blood Glucose Index (LBGI) allow to define the risk of hyperglycemia and hypoglycaemia, respectively. Physical activity plays a main role in the management of T1DM patients. Namely, exercise enhances insulin sensitivity leading to decreased insulin requirement, and improves lipid profile resulting in reduction of cardiovascular risk. Moreover, physical activity promotes the loss of weight.
Objective and hypotheses: To investigate whether or not increased daily life physical activity in the contest of supervised and dedicated environment as summer camps results in changes of risk classes in T1DM patients.
Methods: We evaluated 14 patients (M:F=1,33, aged 8-12 years) who joined a summer camp dedicated to T1DM patients. Accu-Chek® Aviva Nano glucometer was employed to assess daily glucose values. Accu-Chek Smart Pix software was then used to calculate median values, standard deviations (SD), HBGI and LBGI. In each patient measurements acquired during the summer camp were compared to those assessed in the week before, in order to correlate changes in classes of risk with the daily life activity. Fisher test was employed to assess differences.
Results: Statistically significant reduction in LBGI ($P < 0.023$) was observed when values acquired during the camp were compared to the measurements assessed in the normal daily activity. Moreover, absolute glucose determinations and SD tent to ameliorate, although didn't reach a statistically significance.
Conclusions: During this camp children learn to manage insulin requirements and adjust daily doses related to physical exercise, through an accurate glycemic control.

P3-d2-1342 Glucose Metabolism 16

A case of type 1 diabetes mellitus associated with Turner syndrome

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Background: Turner's syndrome is a chromosomal disease frequently associated with autoimmune conditions, including thyroid disease, inflammatory bowel disease and diabetes.
A 11-year-old girl was admitted to the hospital with complaints of polyuria, polydipsia, decreased appetite, weight loss of 8 kg for a few weeks. She was born at term by normal vaginal delivery (birth weight 3400 g) from a healthy mother as first children of the family. There was no consanguinity between the parents. No family history of diabetes was reported. Physical examination at the time of admission revealed a temperature of 36.2 C, a pulse of 99 beats perminute, a respiratory rate of 22 per minute, and a blood pressure of 90/60 mm/Hg. The patient's height was 119 cm (-3,23 SDS) and her weight was 22,5 kg (-2.93 SDS). Calculated body mass index was 15.8 kg/m2 (-0,62 SDS). She was prepubertal at Tanner stage 1.Blood gas analysis showed a pH of 6.7 and HCO_3 2.8 mmol/L. The diagnosis of diabetic ketoacidosis was made, and after appropriate fluid-electrolyte and insulin therapy, multiple dose (4 times daily) insulin injection treatment (1 U/kg/day) was started. Glycosylated haemoglobin A1c was 12,3. C-peptide level was < 0,02 ng/ml.Pancreatic autoantibodies [Islet cell autoantibodies (ICA), glutamic acid decarboxylase antibodies (antiGAD) and anti-insulin autoantibodies (AIA)] were pozitive. On admission she had skeletal abnormalities included a webbedneck, shield chest, and cubitus valgus. Her chromosomal karyotype was 45XO. Echocardiogram was normal. Therefore, the patient was diagnosed as Type 1 diabetes mellitus associated with Turner's syndrome.
Conclusions: It is therefore proposed that all patients with TS and should be investigated for diabetes. Further investigations will be required to determine whether there is a significant association between TS and type 1(DM).

P3-d2-1343 Glucose Metabolism 16

Fatal multi-organ failure with onset of diabetes

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Background: Diabetic ketoacidosis (DKA) is a common presentation for new onset type 1 diabetes. Mortality from DKA is rare and most commonly from cerebral edema. Multiple organ failure (MOF) is an unusual complication of DKA with a mortality rate of 55%. MOF with fungal infection in the setting of new onset diabetes and DKA has not previously been reported in the literature.
Objective: We present a case of a 16 yr old female who died from new onset diabetes presenting in DKA and MOF with overwhelming fungal infection.
Case: A 16 year old female presented with new onset diabetes in DKA and MOF with abnormalities of her lungs, heart, liver, kidneys and leukocytosis. A head computed tomography (CT) obtained due to mental status changes was negative for cerebral edema. Her DKA corrected over 24 hours but the MOF continued to worsen. She was intubated on the first hospital day and required increasing pulmonary support, including high frequency oscillating ventilation and nitrous oxide. She had acute renal failure and underwent continuous veno-venous hemodialysis. Her initial cardiac echocardiogram showed moderate to severely decreased left ventricular function. She also showed liver dysfunction with a peak total bilirubin of 5.2 mg/dl (0.1-1.2) and aspartate aminotranferase of 3681 U/L (10-35). Her white blood cell count peaked at 75.8 x 1,000 (4.8-0.8). A bronchial alveolar lavage grew aspergillosis, candida glabrata and candida albicans and a urine culture also grew candida glabrata and yeast. A vaginal wet prep was positive for yeast. Blood and cerebrospinal fluid cultures were negative. Despite broad antimicrobial coverage her status continued to deteriorate. She developed anisocoria and a repeat head CT showed a new lesion in her brain. The family elected to withdraw care later that day and she died on hospital day 20. Autopsy results are pending and will included on the poster.
Conclusions: MOF is a rare complication of pediatric DKA and has a poor prognosis.

P3-d2-1344 Glucose Metabolism 16

Dietary habits in children and adolescents with type 1 diabetes using continuous subcutaneous insulin infusion vs. multiple daily injections: a descriptive transverse observational study

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Background: One reported drawback was increased weight gain after starting of continuous subcutaneous insulin infusion (CSII).
Objective and hypotheses: In a descriptive transverse observational study, we evaluated dietary habits in 85 children and adolescents, aged 15.5±5.1 yrs, with type 1 diabetes since 7.7±5.9 yrs, using CSII (n=46, 54%) or multiple daily injections (MDI) (n=39, 46%).
Methods: BMI-SDS, insulin requirement, HbA1c, mean HbA1c since diabetes onset, dietary habits using a dedicated software, body composition (Tanita BC-418, IL, USA), blood pressure (BP) and lipid profiles (LP) were evaluated in all subjects.
Results: Data were evaluated according insulin therapy and after stratifying patients according to HbA1c, and are shown in Table 1. BMI-SDS was the same in both groups, as well as the intake of macro and micro-nutrients. However, CSII patients showed a better glycemic control, evaluated as mean HbA1c.

	CSII (n=46)	MDI (n=39)	Significance	HbA1c <7.5% (n=18)	HbA1c 7.5-8.5% (n=35)	HbA1c >8.5% (n=32)	Significance
HbA1c (%)	8.05 ±1.17	8.25 ±1.50	0.495	6.98 ±0.91	7.97 ±0.73	8.99 ±1.48	0.000
HbA1c mean (%)	8.13 ±0.88	8.67 ±1.48	0.046	7.04 ±0.51	7.98 ±0.28	9.56 ±1.06	0.000
BMI-sds	0.20 ±1.03	0.38 ±1.06	0.479	0.30 ±1.10	0.29 ±1.00	0.26 ±1.09	0.933
CHO/ Simple CHO (%)	50±7 / 32±9	52±7 / 36±11	0.230 / 0.119	51±6 / 35±10	51±6 / 33±9	51±9 / 34±12	0.914 / 0.879
Protein (% / g/kg)	17±3 / 1.7±0.7	16±4 / 1.8±1	0.312 / 0.744	16±3 / 1.99 ±0.71	16±3 / 1.77 ±0.86	16±4 / 1.65 ±1.06	0.966 / 0.453
Fat (%) / Saturated fat (%)	33±6 / 10±3	32±7 / 10±3	0.461 / 0.625	33±6 / 10±3	32±5 / 10±3	32±8 / 10±3	0.853 / 0.833
Gylcemic index	54±5	54±5	0.755	55±6	54±5	54±5	0.821
Glycemic load	124 ±44	132 ±65	0.513	139 ±59	129 ±44	119 ±62	0.459
Energy (kcal)	2107 ±595	2151 ±635	0.743	2214 ±651	2157 ±572	2036 ±635	0.548

[Dietary intake in patients with type 1 diabetes.]

Diastolic BP was significantly lower in patients using CSII and in the lowest HbA1c tertile (p=0.015 and p=0.000, respectively), as well as LP (p=0.031 and p=0.015, respectively). Insulin requirement was significantly different only when evaluating HbA1c tertiles (p=0.034).

Conclusions: CSII does not lead to weight gain by itself, but a reinforcement of nutritional education is needed in order to decrease sugar and protein intake in both CSII and MDI patients, while increasing calcium, vit. D and iron intake. CSII helps to have better control than MDI.

P3-d2-1345 Glucose Metabolism 16

Compliance to treatment among children with type 1 diabetes mellitus: experience in Abakaliki

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Background: Management of Type 1 diabetes mellitus (TIDM) poses management challenges in terms of compliance to insulin treatment and blood glucose monitoring in a resource limited setting. There is as yet no study on this in children with TIDM in Abakaliki.

Objective and hypotheses: To asses compliance of children with T1DM to treatment in Abakaliki.

Methods: Cross sectional study of 13 children attending the Paediatric endocrine clinic with type 1 diabetes mellitus between June 2011 and Aug. 2012 was done. All were placed on twice daily injections of pre-mixed insulin 70/30 and regular blood glucose monitoring. Relevant data were retrieved from interviewer administered questionnaire. Analysis done using simple statistics.

Results: From the analysis, 69.3% reported missing their injections from which half frequently missed. Only 30% of them reported never missing their injections. The predominant reason for missing the injections was lack of money to purchase insulin injections (61.5%), others include absence of insulin in the pharmacy (7.7%) and pain on giving injections (7.7%). Only 5(38.5%) patients monitored their blood glucose regularly while 61.5% did not. The main reason reported for this was lack of money to purchase strips. The average HBA1c (%) among the patient studied was 12.8 ±1.6 with a range of 9.9 to 14.

Conclusions: Compliance to treatment in children with TIDM is poor in Abakaliki, hence the poor diabetic control and the major reason for this is poverty.

P3-d3-1346 Glucose Metabolism 17

Paediatric hyperglycaemic hyperosmolar non ketotic syndrome: a rare and dangerous diagnosis which has to be known

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Background: Childhood obesity is a pandemic health care problem. A complication of childhood obesity is type 2 diabetes mellitus. Hyperglycemic hyperosmolar non ketotic syndrome (HHNKS) is a serious complication of type 2 diabetes mellitus and it is infrequently diagnosed till recently in children. The syndrome is characterized by severe hyperglycemia (blood glucose >600mg/dL), a serum hyperosmolality (>330 mOsm/L) and with only mild acidosis (without accumulation of beta-hydroxybutyric or acetoacetic ketoacids, serum bicarbonate> 15 mmo/L).

Objective and hypotheses: Pediatric hyperglycemic hyperosmolar non ketotic syndrome is a rare and dangerous diagnosis which has to be known because of this morbi-mortality (cerebral oedema, rhabdomyolysis and malignant hyperthermia) and the prevalence of childhood obesity

Methods: The patient was an 8-year-old girl of Guadelupian origin. She has a ROHHADNET syndrome (hypothalamic syndrome) causing problems of access to water

Results: Initial laboratory studies showed venous blood gases pH 7.24, PCO2 54 mm Hg, and bicarbonate14 mmol/L, sodium 188 mmol/L (corrected serum sodium, 198 mmol/L), potassium 3.9 mmol/L and chloride 152 mmol/L. Serum glucose was 718 mg/dL; hemoglobin AIc, 9.8%. Urine analysis revealed glucose more than 100 mg/dL; no ketone trace; no blood trace. Calculated serum osmolality was 409 mOsm/Kg. Creatinine was 162 µmol/; urea, 13.5 mmol/L; l. Electrocardiogram showed a hypokalicity. Complications were a major cytolysis (ASAT 1000UI/L, ALAT 550UI/L), a major rabdomyolysis (CPK 90000UI/L) and thrombopenia (platelets 50000/mm3). RMN showed an agenesis of dorsal prancreas. Finally, she presented a MODY 5 with deletion of gene HNF1beta.

Conclusions: Pediatric hyperglycemic hyperosmolar non ketotic syndrome is a rare and dangerous diagnosis. Complications are frequent and serious and must be known for proper care of the patient. Diabetes can begin with HHNKS and an imaging of the pancreas may be necessary.

P3-d3-1347 Glucose Metabolism 17

Impact of insulin pump therapy in children and adolescents with type 1 diabetes on long-term metabolic control: a one year follow-up prospective study

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Objectives: Over the past few years the use of continuous subcutaneous insulin infusion (CSII) has been increasing. The aim of this study was to assess the impact of CSII in children and adolescents with type 1 diabetes (T1DM) on long term metabolic control and acute diabetic complications at initiation of pump therapy and after one year of follow up.

Methods: A total of 21 patients (12M/9F) with T1DM mean age 12.78 ± 2.31 years (4 - 18 years) and disease duration of 5.2 ± 1.9 (3 months - 14 years) participated in the study. Insulin pumps (Minimed 722 Paradigm Real time and Minimed 712, Minimed Medtronic, USA) were used administering short-acting insulin analogue.

Results: After 1 year CSII , a significant reduction in HbA1c levels was observed (8.9 ± 1.6% to 7.6 ± 0.9 % , P= 0.01) from CSII initiation. Total insulin dose required to maintain glycemic control decreased in all patient from 1.2 ± 0.4 to 0.8 ± 0.26 U/kg/day, p=0.00). The frequency of significant hypoglycemia during CSII were less than initiation (4.8 ± 3.5 to 1.6 ± 1.9, P=0.007), hyper glycemic attacks reported were lower especially episodes exceeding 300mg/dl (P=0.00). One patient had an attack of DKA due to catheter trouble, non had mechanical troubles or skin problems. Rate of post prandial hyperglycemia decreased (P=0.09) as a result of adequate insulin bolus on each food intake using Bolus Wizard calculator. The average BMI increased from 18.7 kg/m^2 prior to CSII therapy to 20.1 kg/m^2,P=0.01). The rate of hospitalization due to acute events was less (P=0.03). Patients were satisfied with

decreasing the frequency of injections (one per three to four days).
Conclusion: This prospective study revealed the importance of CSII therapy in sustaining good metabolic control and blood glucose stability for one year. Additional predictive factors for long term benefits of CSII remain to be interpreted from the one year follow -up data onwards.

P3-d3-1348 Glucose Metabolism 17

Frequency of chronic diabetes complications in children with type 1 diabetes and poor glycemic control in Ukraine, treated with continuous subcutaneous insulin infusion vs multiple daily insulin injections (results from 3-year follow-up data)

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Background: In Ukraine frequency of use of CSII increased from 0,5% in 2007 to 7,3% in 2013.
Objective and hypotheses: Were examined 2 groups DM1 children, were treated by CSII and MDII. We studied the dynamic of chronic diabetes complications, HbA1c level before and after 3 y. of different type of treatment. CSII was recommended first of all to children with poor glycemic control, severe chronic and frequent acute complications.
Methods: We created Ukrainian diabetes pumps register, which included all information about children with DM1 0-18 y.o., in particular availability of acute and chronic complications, HbA1c level. We studied a database of 73 children 1-18 y.o., 61,6% - females, duration of DM - 2,5 y. [1,4; 5,0], which were treated by CSII during 3 y. Efficacy of treatment were estimated annually (for acute and chronic complications) and each 3 months for HbA1c. The same register was created for children which were treated by MDII (n=36, 3-18 y.o., 42,9% - females, duration of DM - 4 y. [1,75; 6,0], with a similar glycemic control (p>0,05).
Results:

	Cataract (DC)	Retinopathy (DR1)	Nephropathy 3 (DN3)	Nephropathy 4 (DN4)	Sensor neuropathy (DNs)	Motor neuropathy (DNm)	Nobekur syndrome (SN)	Lypodistrophy (DL)	HbA1c, Me [25;75]
CSII before	1,4	2,7	12,5	1,4	37,5	32,8	4,1	32,9	10,1 [8,3;11,7]
after 3 y.	4,7	4,7	14,3	0	38,1	35,0	0	0*	9,9 [8,9;11,3]
MDII before	2,8	0	33,3	0	8,3	30,5	8,3	36,1	10,2 [9,2;11,6]
after 3 y.	10,0	3,3	33,3	3,3	33,3*	66,7*	10,0	53,3	10,9 [9,2;12,9]

[The frequency of chronic complications, HbA1c (%)]
(* - p< 0,05).

Children treated by CSII had level of HbA1c with tendency to decrease, but it was significantly lower only after 1 y. of treatment (8,9 [8,2; 9,4], p=0,003). Children who were treated by MDII, HbA1c levels did not change significantly despite the increase of the frequency of use insulin analogues of short (70% vs 44,4%) and long action (30% vs 16,7%).
Conclusions: Benefits of CSII were shown in children with DM1 with such chronic complications as DN4, DL and SN despite their poor glycemic control. At MDII group was not observed regress of any chronic complications. Poor baseline HbA1c level may be predictor of poor glycemic control in post-CSII period.

P3-d3-1349 Glucose Metabolism 17

Two families with diabetes mellitus and sensorineural deafness

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Background: Diabetes mellitus (DM) is one of the most common chronic disorders of children. Type 1 DM is the most common form of diabetes in children. Rarely DM is associated with other systemic features. DM and sensorineural deafness (SD) are features of rare syndromes like Wolfram syndrome, Rogers syndromes and Mitochondrial DM. Wolfram syndrome (also known as DIDMOAD syndrome) is caused by los of function mutations in the WFS1 gene and the clinical features include diabetes Insipidus, DM, optic atrophy and SD. Rogers syndrome is caused by mutations in the SLC19A2 gene and is characterised by the occurrence of megaloblastic anaemia, DM, and SD. Mitochondrial DM is caused by mutations in MT-TL-1 gene and patients have DM with mitochondrial disease.
Patient and methods: We report two unrelated consanguineous families with three affected children with DM and sensorineural hearing loss. These patients do not have any developmental or eye abnormalities and no mental or neurological disorders and no learning disabilities. Genomic DNA was extracted and amplified using polymerase chain reaction and the exons and the exons-introns boundaries were sequenced for possible mutations in WFS1, SLC19A2, and MT-TL1.
Result: No mutations were identified in the coding regions of the genes WFS1, SLC19A2, MT-TL1 to explain the clinical phenotype of these patients. This suggests that there might be another unidentified genetic aetiology in these patients to account for the phenotype.
Conclusion: In the two families mutations in the known genes (WFS1, SLC19A2, and MT-TL1) have been excluded which cause DM syndromes associated with SD. This suggests that these patients may have other novel genetic causes for DM and SD. Further work including homozygosity mapping and whole exome sequencing are in progress to find the genetic mechanism of DM and SD in these patients.

P3-d3-1350 Glucose Metabolism 17

Alstrom syndrome: case report of two new cases

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Background: Alstrom syndrome (AS) is a rare autosomal recessive disorder characterized by retinal degeneration, childhood obesity, hearing loss and non-insulin-dependent diabetes mellitus. The primary cause of mortality is dilated cardiomyopathy among young patients and renal failure among older subjects. A diagnosis is usually established on the basis of clinical features and molecular genetic analysis of ALMS1 gene can be used to confirm the diagnosis.
There is no specific therapy for AS but, early diagnosis and multidisciplinary follow up intended to anticipate and detect the complications, can moderate the progression of the disease. We report the clinical and molecular findings of two new cases of AS.
Case study 1, presented at 4 years of age with poor vision, nystagmus and bilateral sensorineural hearing loss. At 10 years she developed non-insulin-dependent diabetes and she was put on metformin. She showed also hypertriglyceridemia (1700mg/dL); heart US revealed mild bilateral atrial dilatation and mild left ventriculus dilatation; at the abdomen US: haepatomegalia with haepatic steatosis.
Genetic sequencing of ALMS1gene did not reveal any variation.
Case study 2, presented at 3 years with poor vision and nystagmus. Heart US revealed mild left ventriculus dilatation. He was obese but he did not develop diabetes. He revealed a known genetic mutation in ALMS1 gene. His sister at 1 month of life was diagnosed with dilated cardiomyopathy, absent foveal reflex and retinopathy. At three months she died because she developed a severe respiratory failure.

Conclusions: Clinical diagnosis of AS in case 2 was confirmed by genetic analysis, but not in case 1. However case 1 presented with one major and three minor criteria that are consistent with the diagnosis of AS. We confirm that some patients with clinical diagnosis of AS do not present any gene mutation in ALMS1 and more studies for other genetic cause of AS should be considered to reduce misdiagnosis.

P3-d3-1351 Glucose Metabolism 17

Glucagon rescue for emergency and surgical rescue in children with congenital hyperinsulinism

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Background: Unpredictable hypoglycemia it's a rare complications in the ambulatory settings of childrens with hyperinsulinism in medical treatment.
Objective and hypotheses: Traditionally diabetic patient's with hypoglycemia due to insulin are treated with glucagon dose, the physiopatologic cause it's the same, and the hyperinsulinemic patien'ts usually shown low glucose values in sicknes days.
Methods: We describe the evolution of one patient with congenital hyperinsulinism trated with glucagon recue during surgical procedure for gastrostomy due to severe imnpared succion and deglution for her hypotonia.
Results: The preoperative and operative results are shown also one hypoglucemic event treated for her mother in rural area with minidose of glucagon.
Conclusions: In patients with hyperinsulinism, mini dose of glucagon in the context of adecuate follow up and dose of diazoxide are important part of the care of this patients.

P3-d3-1352 Glucose Metabolism 17

An infant with transient hypocortisolaemia and hyperinsulinism: a case report

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Background: Neonatal hypoglycemia which increase mortality and morbidity in a life-threatening problem. We reported a case of with recurrent hypoglycemia.
Case: Eight-day-old male patient was admitted to our clinic with refractory hypoglycemia. A term, 37 week baby with birth weight of 4100 g was delivered by cesarean section. Baby had multiple episodes of asymptomatic hypoglycemia starting on day 1 of life, until day 8. Maximum glucose infusion reached was upto 12 mg/kg/min, steroid and diazoxide were added. Hormonal evaluation during hypoglycemic episode revealed increased insulin level 24 mU/L, serum cortisol level was significantly low 0,2 µg/dl. ACTH stimulation test was performed, and presence of hypocortisolemia was confirmed. Urinary ketones were absent. MRI brain and USG abdomen were normal. Repeat serum cortisol level during euglycemia was normal. The treatment continued with diazoxide.
Conclusions: Hyperinsulinism and hypocortisolism in newborn are important causes of severe and recurrent hypoglycemia. In infancy with recurrent episodes of hypoglycemia it should be considered presence of hyperinsulinism and hypocortisolemia together.

P3-d3-1353 Glucose Metabolism 17

Incidence of child immigration and a public awareness campaign in diabetic ketoacidosis debut in Spain

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Introduction: In the last 10 years the incidence of diabetes in children appears to have increased dramatically in our region. Also was demostrate the higher prevalence of ketoacidosis (DKA) to debut in Spain (up to 5 times higher) than in other neighboring countries (study ESPE). These data launched awareness campaigns from Primary Care from the year 2008. Also in the past 5 years have been increased among children from other countries with lower awareness and health literacy regarding the monitoring of the child from the Primary Medical Centers
Objective: To assess the changes occurring in the debut epidemiology of children suffering from type 1 diabetes in our country in relation to the previous variables in the last 10 years.
Methods: Income diabetic in our Hospital debut from 2002 to 2012. The comparative statistical analysis ANOVA for paired groups and chi2. Variables were assessed sex, age, DKA criteria and geographical origin. Years were studied separately and grouped in five years 2002-07 and 2008-12.
Results: 93 under 14y type1 DM debuted in our Hospital. Incidence 1/3.952 children / year. 49% were children (46/93) and 48% DKA (45/93). Predominant age range 3-10a (42%), followed by adolescents (31%) and preschoolers (23%).9% (8/93) were foreigners. Prevalence rises from 1/5.820 children / year 1/3.472 children / year ($p = 0.002$), and DKA goes from 65 to 35% ($p = 0.001$), the pubertal age range drops from 40 to 24% ($p = 0.01$), which amounts the age range of pre-school from 12 to 32% ($p = 0.005$), comparing the two time periods, as well as the 8 foreign children concentrate on the latter. The group of Spanish children DKA from 65% to only 15% in both periods of five years, while 100% of foreign children debuted in DKA.
Conclusion: The incidence of type 1 DM has increased in our area parallel to the arrival of children from other backgrounds. Earlier diagnosis and without DKA is possible, but the group of immigrant children remains by its peculiarities social.

P3-d3-1354 Glucose Metabolism 17

Uncontrolled diabetes: a difficult mother or a mother in difficulty?

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Background: Young children with diabetes (YCD) are a particularly vulnerable group because they are reliant on adult providers for their management needs. Healthcare professionals have a responsibility for the needs of the child, targeting good glycaemic control (GC) to improve quality of life and reduce the risk of complications. It can, however, be a difficult balance to provide support for the families who struggle and engage them in their child's management whilst also considering at what stage the safeguarding team and social services should be involved.
Case report: We report a 6-year-old girl with type 1 diabetes since the age of 2½ years. She has had uncontrolled diabetes throughout with HbA1c ranging between 10.7% and 15.7%. A number of social factors have influenced her diabetes control including parental separation, maternal mental health concerns and lack of family support. Each time these issues have been addressed and also when care has been provided by grandparents for short periods, a transient improvement in GC is noted. However, this is always short-lived and there are ongoing concerns about mother's lack of engagement with the diabetes team.
Discussion: This case, and many similar cases, continue to pose significant challenges for diabetes teams. A balance should be kept between providing adequate support for such families against a possible need for safeguarding children. It can be difficult to identify those families who are struggling and distinguish them from those who are neglecting their YCD. As a team we recognise the importance of considering safeguarding issues in such situations but also feel that each case should be assessed individually.

Conclusions: Ultimately, using a patient centred approach; if there is no improvement in diabetes control despite taking all measures to support mothers/families that have difficulty in managing their YCD, it becomes difficult to justify not involving the safeguarding team.

P3-d3-1355 Glucose Metabolism 17

The level of knowledge on diabetes of children and adolescents with type 1 diabetes mellitus (DM) in Uzbekistan

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Aim: To define the impact of knowledge of children and teenagers about type 1 DM on disease control and compensation level for optimization of work of Diabetes School.
Materials and methods: Children(550) and adolescents (380) with type 1 DM and their parents were objective group of our work. Children were 9±1.2 years old, durarion of diabetes 6±1.8 years. Adolescents were 15±2.2 years old with DM duration of 8±1.3 years. The assessment of effectiveness of education using new structural program of training in diabetes schools (DS) was performed by quantity of right answers on questions about DM, its compensation, and self-control. HbA1c was tested to estimate compensation of carbohydrate metabolism in all examined people.
Results: The average knowledge of children with type 1 DM was 65%, the best results were got from patients of Samarkand and Navoi regions (80% of true answers), the worth - in Namangan and Djizakh regions (45%). Children with compensated DM (HbA1c < 7.5%) answered in average on 75% (from 60 to 80%) questions correctly, which is significantly higher then the level of knowledge of children with decompensated DM. The average percentage of true answers in the Republic among adolescents with compensated DM was 73%. Adolescent with decompensated DM gave correct answers to 53% questions. However in some regions (Navoi, Samarkand and Tashkent city) adolescents with HbA1c level > 7.5% answered correctly on 65% questions. At the same time, these patients did not obtain goal HbA1c level, which could be due to psychological factors of adolescent period, to increase demands in insulin in this period without agreeable dose correction, and other factors.
Conclusion: In the Republic the level of knowledge of children and adolescents with type 1 DM is satisfactory, being good in Samarkand and Navoi regions; the worst results were in Namangan and Djizakh regions. The higher the level of knowledge of patients on self-control, the better DM compensation.

P3-d3-1356 Glucose Metabolism 17

Management of a restrictive eating disorder in an adolescent male with insulin dependent diabetes mellitus (IDDMI)

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Introduction: This case highlights the course and successful outcome of an adolescent male with IDDM and a restrictive eating disorder.
Case study: A 14 year old boy with known IDDM for 9 years presented in routine diabetes follow up clinic having made healthy life changes. He had embraced exercise with passion and had shown weight loss achieving some dramatic changes. His HbA1C% however had increased from 7.6 to 9.3% in less than 3 months and he was having regular hypoglycaemic episodes during exercise. A detailed dietary history prompted a referral to the diabetes dietician at the time with close monitoring of his weight fortnightly at home. However the patient was admitted to hospital within the following month as there were growing concerns of ongoing weight loss cumulating to a total of 9 kg over 6 months. The patient demonstrated disordered and concrete thinking around the need for weight loss and had dramatically reduced his food intake. He appeared fixated on exercise. He had frequent hypoglycaemia and refused to treat these episodes due to fear of 'getting fat'. There was severe dietary indiscretion and repeated insulin omission. His insulin dose had steadily decreased to 0.74U/kg/day. Screening bloods did not demonstrate an underlying physical cause for his weight loss. He was admitted in conjunction with the mental health team and received intensive dietician support, social work and psychology input for low mood. He was prescribed set meal plans and one to one nursing. After the 3 month admission for stabilisation and management he had follow up to review sustaining the discharge dietary and lifestyle modification at home.
Conclusion: Review of the literature and this case highlight that disordered eating attitudes and behaviours are associated with impaired glycaemic control. We suggest that screening for clinical and subclinical eating disorders systematically in children and adolescents would help identify high risk individuals.

P3-d3-1357 Glucose Metabolism 17

The effect of automated bolus calculators on HbA1c in children with type 1 diabetes in Macclesfield

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Background: Previous studies have shown that using Automated bolus calculators (ABC) in type1 diabetic children showed noticeable reduction in HbA1C(1). Furthermore, it showed reduction in post prandial blood glucose level(2) and glucose variability(3) for those children treated with insulin pumps. Data from adults has already shown improvement in HbA1C following usage of ABC(4).
Objective: To confirm the effect of ABC on HbA1C in children with type1 diabetes who are on multiple daily insulin injection regimes in our unit.
Methods: This is a cross-sectional study. We have collected the data via Accu-check software and by reviewing the case notes. HbA1C was measured before and after ABC use. Some of the patients were started immediately on ABC following their diagnosis with diabetes and others were started later after they showed poor glycaemic control.
Results: 22 patients were identified (age 6-15 years, M:F 10:12) with a duration of diabetes before being started on ABC 0-11 years, but with median of 7.5 months. The HbA1C was monitored over an average period of 18 months (4-30 months). There was an improvement in HbA1C in 59%, their average age was 12 years (M:F 6:7). There was a 3% (33 mmol/mol) reduction in median HbA1C for this group post ABC use. (Median HbA1C pre ABC 90.9 mmol/mol (10.8% ±2.4) while post ABC was 58 mmol/ml (7.8% ±0.9). 9 patients had a raise in their HbA1C by 1% (pre ABC 8.4% ±1.27 and after 9.4% ±1.34). Their average age was 13 years (M:F 4:5). They were less frequently checking their blood glucose (average of 3.5 times per day, versus the other group 4.8 times per day) and hence using the ABC less often.
Conclusion: Our results show that ABC's work best for children and young people who check their blood sugars more often. These results are really encouraging towards finding out about the role of other relevant factors e.g. education and training which might play a role in improving control. RCT with larger patient numbers is needed.

P3-d3-1358 Glucose Metabolism 17

Clinical study of behavioral problems among children with type 1 diabetes mellitus (T1DM) in Minia governorate, Egypt

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Background: Egypt has an intermediate incidence of T1DM (5% - 9.99%) between Arab countries. Diabetes impacts the life style, personality, overall emotional & physical well being of the child. Children with a chronic disease are twice as likely as healthy children to have a psychological problem
Objective and hypotheses: To trace out the frequency of behavior disorders among children with TIDM and to correlate them with different demographic and metabolic control

Methods: This study was a cross sectional study carried upon fifty children with T1DM who attended Diabetes outpatients' Clinic, Minia University Children's Hospital, Minia governorate. Another fifty children age and sex matched from the same families were taken as a control group.Diabetic patients were subjected to: complete history taking, clinical examination, laboratory investigations.All studied children were subjected to the Revised Behavior Problem Checklist (RBPC) to rate problem behavioral problems.
Results: Based on RBPC ratings: the frequency of behavioral disorders was significantly higher in diabetic children than the control (P=0.001). Motor excess was the commonest disorder followed by socialized aggression and attention problems. Males were more significantly affected than females.The poor controlled patients significantly had different behavioral disorders.
Conclusions: Behavioral problems were significantly presented in children with T1DM.

P3-d1-1359 Growth 7

Children of mothers with pre-gestational and gestational diabetes tend to be overweight at age 17

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Background: Knowledge on adult height and weight of children born to diabetic mothers is scant.
Objective: To compare height and weight of children born to diabetic mothers with those of children born to healthy mothers at birth and at age 17.
Methods: We identified all full term neonates of diabetic mothers born between 1987 and1993 in the Rabin Medical Center in Israel. The control group included neonates born to healthy mothers during the same period. The birth sizes (length and weight) and height, weight and BMI at age 17 as measured at the recruitment centers of IDF, were compared between groups.
Results: There were 447 children (235 males) from mothers with gestational diabetes(GDM), 97 children (51 males) from mothers with pre-gestational diabetes (PGDM) and 544 children (265 males) in the control group. At age 17 we were able to track 674 adolescents (61.95% of the original groups).

Gender	Parameter	GDM	PGDM	Control	p
Males	N	159	34	198	
	Birth length	49.7±2.0	49.3±1.8	49.6±1.6	0.37
	Birth weight	3423±527	3451±535	3344±372	0.18
	BMI≥85th percentile at age 17	27.0%	26.5%	16.1%	<0.01*
Females	N	113	23	147	
	Birth length	48.7±2.0	48.6±1.7	48.9± 1.9	0.61
	Birth weight	3230±510	3210±364	3228±324	0.98
	BMI≥85th percentile at age 17	15.9%	34.8%	15.6%	0.44*

[Anthropometric indices at birth and at age 17]
* Between the control group and the 2 other groups combined

There was no statistically significant difference in birth length or weight between the groups in both genders.
Conclusions: Our study shows that improved treatment of diabetes during pregnancy in the 1990's resulted in normally sized newborns. Nevertheless, children born to diabetic mothers tend to be overweight adolescents and are at risk to develop future metabolic syndrome.

P3-d1-1360 Growth 7

Establishment and validation of a new cut-off concentration for growth hormone stimulation tests in children

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Background: Currently cut-off concentrations for GH-stimulation tests in children are not justified by clinical studies. Departments for pediatric endocrinology use different stimulation tests, dissimilar assays and only arbitrary cut-off levels.
Objective and hypotheses: We established a new cut-off concentration to be used for interpretation of GH stimulation tests in pediatric patients.
Methods: Serum hGH concentrations of stimulation tests of 52 children and adolescents were used that were non-GH deficient which was proven by auxological measurements and test results. We established a new cut-off value for the iSYS fully automated immunoassay (IDS). We then validated this cut-off by a collective of 44 patients of the cohort which were diagnosed as GH deficient (GHD). The iSYS data were compared with results of an isotope dilution mass spectrometry (ID-MSMS) used as a "gold standard". Finally, iSYS cut-off data were transferred to kits from other manufacturers.
Results: hGH values of serum samples were stable for more than a decade, if stored at -80±5°C. The new cut-off value for hGH stimulation was 7.23 ng/mL (5th percentile) in sera of none-GHD children using the new iSYS method (max. GH-secretion 12.96 +-5.02 ng/ml). In addition we compared and validated the new iSYS cut-off by a collective of children with GHD (max. GH-secretion 4.80 +- 2.95 ng/ml). Cut-off values were transferred to 7 different assays: 8.06 ng/mL (IL-2000), 7.93 ng/mL (AutoDelfia), 6.66 ng/mL (Liaison), 5.90 ng/mL (RIA Tuebingen), 5.66 ng/mL (Mediagnost), 5.64 ng/mL (DxI) and 4.60 ng/mL (BC-IRMA).
Conclusion: We provide a new cut-off concentration to be used for interpretation of GH stimulation tests in pediatric patients. This cut-off value can be transferred to other kits and will be a helpful tool in the future to differentiate between GH-deficiency and adequate GH-secretion during childhood and adolescents.

P3-d1-1361 Growth 7

Do children with 1p36 deletion deserve growth hormone treatment?

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Background: Monosomy 1p36 is considered to be the most common subtelomeric microdeletion syndrome. Clinical features include distinct facial appearance, short starure, cardiac involvement, sensorineural hearing impairment and hyperphagia. Almost all patients have mental retardation and speech delay.
Objective and hypotheses: We report a case of 1p36 syndrome with growth hormone deficiency and the efficacy of growth hormone replacement therapy.
Methods: The index patient is a female born at term by phenotypically healthy, non-consanguineous parents. Shorty after birth she was diagnosed with congenital hypothyroidism by neonatal screening test and started on thyroxine replacement therapy. She was followed for idiopathic mental retardation and developmental delay. At the age of 6 years' she was referred for evaluation of short stature and obesity. On examination the patient's height was 102.7 cm (< 3rd percentile), her weight was 22 Kg (50th percentile) and BMI 20.85. We performed clonidine and glucagon stimulation tests, which revealed severe growth hormone deficiency (GHmax 0.92 and 2.04 ng/dl respectively). Brain MRI scan revealed prominent ventricles with no hypothalamic-pituitary pathology. Moreover, we proceed to cytogenic and molecular analysis with multiplex ligation-dependent probe amplification (MLPA) which identified the

deletion 46,XX, del(1)(p36.2). Replacement therapy with rhGH was started.
Results: On follow-up the patient's height gradually improved. Her weight remains the main concern although it is improving. Her current height is on 10th centile and her weight on 90th centile.
Conclusions: Short stature is a common feature in patients with 1p36 deletion syndrome. However, to the best of our knowledge, growth hormone deficiency and treatment has not been reported previously. The current case is probably widening the knowledge in that field.

P3-d1-1362 Growth 7

Absence or reduction of the physiological catch-up growth after adoption in internationally adopted children exposed to alcohol in utero

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Background: Usually after adoption catch-up growth is observed in children.
Objective and hypotheses: We aimed to assess whether this post-adoption catch-up growth is also presented in children exposed to alcohol during pregnancy.
Methods: We measured at arrival and after 1-3 years 64 adopted children from countries of the former USSR. Twenty-nine (45%) presented clinical signs or had a history of prenatal alcohol exposure in utero (FAS/FASD), thirty-five were considered as controls. Height (Ht), BMI and head circumference (HC) data (expressed as SDS), subdivided according to sex, were analyzed and compared within and between the two groups.
Results: Ht SDS, BMI SDS and HC SDS were different in the two groups at arrival ($p< 0.001$) and at follow-up ($p< 0.001$). Ht SDS values increased from baseline in both groups but was more consistent in controls ($p< 0.001$ vs. $p< 0.05$). HC SDS were different in the 2 groups ($p< 0.001$) at arrival, but while controls showed a mild increase in HC SDS after adoption ($p< 0.05$), the FAS/FASD group did not show any change. BMI SDS were significantly different at arrival in the two groups, but did not improve in either group at follow up. A further subdivision of exposed children into severe (FAS, n=10) and mild (FASD, n=19) forms showed that the latter presented a slight improvement in Ht SDS ($p< 0.05$). Moreover two FAS children, with partial GHD, did not respond to GH therapy.
Conclusions: Controls and FAS/FASD children increased significantly their original Ht SDS after arrival. While controls reached a final height within normal range, the FAS/FASD group remained in the lower range (< 10° centile) and 20% fell below -2 SDS. Controls showed a significant increase in HC SDS while the FAS/FASD group did not. In conclusion, our study demonstrated lack (FAS) or impairment (FASD) of post-adoptive catch-up growth, interestingly both in Ht SDS and HC SDS.

P3-d1-1363 Growth 7

GH deficiency in patients with Noonan syndrome: growth response to rhGH therapy related to the genotype

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Background: Noonan Syndrome (NS) is an autosomal dominant disorder characterized by short stature, dysmorphic features, congenital heart defects and other anomalies. Familial or *de novo* mutations in PTPN11, RAF1, SOS1, KRAS, and NRAS are detected in 60-75% of cases.
Objective and hypotheses: The aim of this study was to evaluate the GH secretion and the response to rhGH therapy in NS patients with GH deficiency (GHD) searching for a possible relationship with the genotype.
Methods: GH secretion was evaluated in a subcohort of 10 patients (3 males and 7 females, mean age 8.1 years, range:2.2-14.0 years) out of 35 cases with NS, showing a stature below the 3rd centile or a height velocity deceleration. Nine of them showed a GHD which was partial in 8 out of 9 and total in the remaining case. Eight patients were treated with rhGH at the standard dose for at least 2 years. Four out of 8 cases were PTPN11+, 2 cases SOS1+ and the remaining 2 cases were mutation-negative.
Results: Before treatment the mean height SDS (H-SDS) was: -2.90±0.59 in PTPN11+, -2.2±0.75 in SOS1+ and -2.81±0.92 in mutation negative patients. A H-SDS increase was detected in all three groups (H-SDS -2.75±0.34 and ΔH-SDS 0.15±0.55 in PTPN11+, H-SDS -2.1±1.14 and ΔH-SDS 0.11±0.39 in SOS1+, H-SDS -1.12±0.64 and ΔH-SDS 1.69±1.55 in mutation negative). In three patients (2 PTPN11+ and 1 SOS1+) who have reached the final height the H-SDS was higher than the one before treatment. In SOS1+ patient the improvement was higher than in PTPN11+ H-SDS (-1.2±0 and -2.48±0.28 respectively). Although GH therapy, the final height in the two PTPN11+ patients remained below the 3rd centile, while it was between the10th and 25th centile in the SOS1+ patient.
Conclusions: This study shows a GHD in 90% of this subcohort of NS with stature below the 3rd centile or a height velocity deceleration. SOS1+ and mutation negative patients showed a better response to therapy than the PTPN11+ ones.

P3-d1-1364 Growth 7

The long-term effects of recombinant growth hormone therapy (rhGH) on growth and glucose homeostasis in poorly growing children with inflammatory bowel disease (IBD)

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Background: Therapy with rhGH in children with IBD may be associated with a short-term improvement in linear growth and altered insulin sensitivity.
Objectives: To investigate the effects of prolonged rhGH on growth and glucose homeostasis in children with IBD.
Methods: Of 20 IBD children (15M) with a median age of 14.4yr (range,8.9,16.2) who received rhGH (0.067mg/kg/d), 4 were treated for 6 months, 2 for 12 months, 9 for 24 months and 5 for a median of 44months (41,58). Anthropometric data were collected at 1yr before starting GH(T-12), baseline(T0), 12 months (T12), 24 months (T24) and at maximum follow-up(MF). Metabolic assessment was performed at T0, T12 and T24.
Results: At T-12, the HtSDS of the whole cohort was -2.3(-3.9,-0.9) compared to a MPHSDS of -0.3(-1.1, 0.8) ($p< 0.0001$). For the 12 month rhGH subgroup (n,16), HtSDS improved from -2.7 (-3.8,-1.4) at T0 to -1.8(-3.2,-0.8) atT12 ($p=0.02$). In this subgroup, ΔHtSDS improved from-0.3 (-1.8,0.3) at baseline to 0.6 (0.06,1.06) at T12 ($P=0.000$). AtT24, HtSD Sin the 24 months rhGH subgroup (n,14), increased from -2.8 (-3.8,-1.4) at T0 to -1.9 (-3.2,-0.8) at T12 ($p=0.04$) and -1.6 (-2.4,-0.2) at T24($p=0.003$). Median ΔHtSDS improved from -0.3 (-0.7,0.3) to 0.6 (0.2, 1), at T12 and 0.5 (-0.05,0.9) at T24($p=0.000$). At MF for the whole cohort, at the age of 17.7yr (12.8,21.8) HtSDS was -1.0 (-3.7,0.1) ($p=0.0002$) compared to T0. No significant alterations were observed in fasting glucose for whole cohort which was 4.7mmol/l (3.5,5.5), 4.8mmol/l(3.0,6.7) and 5.0mmol/l (4.0,7.3) at T0, T12 and T24, respectively. Fasting insulin for those who had rhGH for 12 months was 4.5mU/l(1.9,19) and 7.9mU/l(3.5,15.8) at T0 and T12, respectively ($p=0.01$). For those who received rhGH for 24 months, fasting insulin at T0, T12 and T24 was 4.3mU/l (1.9,19), 7.7mU/l(3.5,15) ($p=0.03$) and 8.4mU/l(2.3,24) ($p=0.09$), respectively.
Conclusion: The short-term growth promoting effects of rhGH are sustained over a longer period. Glucose homeostasis is not markedly affected but should be monitored during therapy.

P3-d1-1365 Growth 7

Sleep pattern and growth hormone secretion during sleep in short children with and without growth hormone deficiency

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Aim: We aimed to investigate the differences of sleep pattern and growth hormone (GH) secretion during sleep between short children with and without GH deficiency using two GH stimulation tests [L-dopa and insulin tolerance test (ITT)]. Additionally, we aimed to determine relationship between sleep stage and GH secretion during sleep.
Subjects and methods: Sixty eight children with short stature [height standard deviation score (SDS)< -2] age ranged 10-15 years were included in this study. Forty three of them were diagnosed as GH deficiency using two GH stimulation tests. The rest of 68 children had no GH deficiency. All children included this study were pubertal. Polysomnography was carried out to all children. GH secretion during sleep was studied in all children. Samples were collected through a per half hour blood withdrawal pump while sleep was recorded.
Results: Weight SDS in children without GH deficiency were significantly lower than those in children with GH deficiency (p=0.029). Sleep characteristics and GH levels during sleep did not differ between two groups (p>0.05). No significant difference was found in terms of sleep stage between two groups. There was negative significantly correlation between mean GH levels during sleep and wake time during sleep (r=-0.26, p=0.03) and positive significantly correlation between mean GH levels during sleep and growth rate (r=0.26, p=0.03).
Conclusions: Sleep characteristics and GH secretion during sleep can not change in short children with and without GH deficiency. Nevertheless, sleep pattern affects GH secretion during sleep. Decrease of wake time during sleep may cause increase of GH section during sleep. Thus, growth rate may increases.

P3-d1-1366 Growth 7

Celiac disease in idiopathic short stature children

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Background: Short stature is one of the most common disorders in Iranian children.
Objective and hypotheses: According to bread is rich in Gliadin protein and it is one of the most common foods in our community, we designed this study to evaluate the frequency of Celiac disease in idiopathic short stature children without gastrointestinal symptoms in Northwest Iran.
Methods: In this descriptive analytic study we studied children lower than 12 years old with short stature and without gastrointestinal symptoms. After achieving inclusion criteria enrolled in this study, total serum IgA was measured in all caces, and IgA deficient cases were excluded. IgA and IgG antitissue transglutaminase (TTG) antibodies, IgA and IgG anti endomysial antibodies (EMA) were measured. In children with any of the antibodies over than 20 IU/ml underwent small intestinal biopsy. The biopsy samples were classified according to Marsh criteria.
Results: A total of 200 children(93 boy and 107 girl) were studied. Anti EMA in 2 cases (1%), anti TTG in 6 cases(3%) and both antibody was positive in 8 cases (%4). Characteristic histological changes was compatible with celiac disease in 5 cases (2.5 %). There was no significant difference in comparison of chronological age, bone age, height z-score, weight , growth velocity between children with and without celiac disease.
Conclusions: In this study 2.5 percent of short stature children without gastrointestinal symptoms had celiac disease.So it is important to mention that short stature can be the only symptom of celiac disease.

P3-d1-1367 Growth 7

Intermittent rhGH treatment as an alternative to rhIGF-I in a boy with *GH1* macrodeletion

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Introduction: *GH1* deletion leads to severe short stature and the eligible treatment with rhGH may fail due to antibody formation. In these cases, the treatment of choice is rhIGF-I.
Case study: We report on the case of a male patient with *GH1* macrodeletion, with GH nocturnal profile showing no GH peak. His height was -6.2 SDS at the age of 4 years when rhGH was prescribed. During the follow up, after an initial catch up, was observed a falloff in growth and three years later his annual height increment was zero and serum IGF-I concentration undetectable. Irregular use was excluded and the IGF-I generation test showed no IGF-I increment. The rhGH daily dose was then raised, with no growth response. Although we realized the need of rhIGF-I therapy, it was not available in our country. His longitudinal evaluation revealed that his growth velocity was higher after periods without rhGH injections. Theses interruptions initially occurred as a patient initiative due to his disappointment with the poor therapy results. Latter we decided to plan regular breaks on the rhGH replacement. He reached complete puberty at the age of 18 years with bone age of 14 years. He is now 20 years old and is still growing under the regime of intermittent rhGH injections. Mean and peak height velocity were 4 and 7 cm/year, respectively. His current stature of -5.6 SDS (140 cm) is expected to improve considering the delayed bone age.
Conclusion: We think that in this patient growth rate was compromised by GH antibodies formation after rhGH therapy introduction. The intervals without treatment probably led to antibodies washout and consequently restored GH action and height gain.

P3-d1-1368 Growth 7

Growth hormone deficiency in a patient with Gitelman syndrome

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Background: Growth retardation is one of the major complications in children with primary tubular disorders. Few cases have been described showing the association between growth hormone deficiency (GHD) and Gitelman syndrome (GS), a rare autosomal recessive hereditary salt-losing tubulopathy.
Objective: A 8.3 yrs old girl from a non-consanguineous family was admitted to our Pediatric Unit for short stature. HE was in good health and no symptoms were referred.
Methods and results: At the first evaluation HE showed: height 116.0 cm (-2.13 SDS) with mid-parental height of 156.0cm (-1.24 SDS), weight 23 Kg (10th-25th centile) and pubertal stage 2 according to Tanner. Laboratory findings showed: IGF-I 77.6 ng/ml (-1.7 SDS), normal thyroid function, negative results on test for celiac disease, normal ACTH and cortisol levels. Adolsterone levels were 398 pg/ml. HE showed hypokaliemia (2.8 mEq/l), with normal magnesium, calcium and sodium levels. Peak GH after stimulation with arginine and insulin was suggestive of GHD (peak GH 1.4 ng/ml in both cases). According to Greulich and Pyle method the bone age was 8 yrs. Magnetic resonance imaging of the hypothalamic-pituitary region was normal. The association of hypokalemia and hyperaldosteronism suggested GS disease or Bartter syndrome III. Thus, sequence analysis of the entire coding region and intron-exon boundaries of CLCNKB and SLC12A3 genes revealed the mutation Pro643Leu in SLC12A3 gene in homozygosity, confirming the diagnosis of GS. The mutation was confirmed in heterozigosity in both parents. GH replacement therapy was started at the dose of 0.030mg/kg/day, with satisfactory growth response. Hypokaliemia was treated by oral potassium and after 12 months oral magnesium supplementation was required.
Conclusions: In the present case, short stature represents the early manifestation of GS. Although short stature may be a feature of GS, this case report suggests the opportunity to explore possible GHD in these children.

P3-d1-1369 Growth 7

Height and weight at 6 years of age in children born preterm: preliminary results

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Background: Children born prematurely might experience a period of growth restriction just after birth and catch-up growth can be slow and progressive. Early catch-up growth has shown to be beneficial for neurodevelopmental outcome, but concern exists that increased rates of catch-up growth may be associated with obesity and the later development of metabolic syndrome.
Objective: To evaluate height and weight development of preterm infants at age of 6 years.
Methods: 62 children (31 girls) born preterm (gestational age 32.9 ± 3.1 weeks) were evaluated with a mean age of 6.5 ± 0.3 years. Weight, height and body mass index (BMI) were evaluated and Z scores were calculated using the reference of NCHS, 2000. According to Z score, overweight was considered if BMI between +1 and +2, and obesity if BMI ≥ +2. Underweight and short stature if respective Z scores for weight and height ≤ -2. Small for gestational age (SGA) was defined as Z score for birth weight and/or birth length < -2 (Babson & Benda, 2003).
Results: Six children (9.7%) were born SGA and one child was large for gestational age (LGA). The mean Z score for birth weight was -0.30 ± 0.96 and the average birth length was -0.42 ± 1.10. The mean weight, height and BMI Z scores at 6 years of age were, respectively, -0.60 ± 1.28, -0.37 ± 0.97 and 0.22 ± 1.20. Three children were underweight, one of which also had short stature. Two had short stature, both born SGA, and 16 were at risk for short stature (Z-score between -1 and -2). Four children were obese, including the one born LGA, and two were overweight.
Conclusions: In the present group of children born preterm, weight and height were appropriate for most of them at 6 years of age. However, some children evolved with short stature, underweight or obesity. A detailed assessment of conditions at birth and during the first years of life is needed to identify children at risk for these changes.

P3-d1-1370 Growth 7

The high incidence of oligosymptomatic gastrointestinal tract diseases in children with short stature of different etiology

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Background: Both endocrinological and gastrointestinal diseases (GIDs) may affect the growth velocity in children. In some cases, the symptoms of the GIDs may be scarce or poorly expressed.
Objective and hypotheses: The aim of the study was to evaluate the incidence of oligosymptomatic GIDs in children with short stature using some simple tests to detect them in routine pediatric diagnostic of short stature and applying some more advanced tools in cases needed.
Methods: Analysis comprised 121 (53 girls and 68 boys) short children (height below -2.0 SD), aged 5.5-14.5 years (mean: 10.37±3.28 years) with idiopathic short stature (ISS, n=101) and with growth hormone deficiency (GHD, n=20). All children were diagnosed for: celiac disease (CD), cystic fibrosis (CF), *Helicobacter pylori* (HP) and *Ascaris* sp. (Asc) infections, *Candida albicans* (Calb) colonization, lactose malabsorption (LM) and inflammatory bowel disease (IBD).
Results: In 78.5% of short children one or more GIDs were diagnosed, with the highest incidence: Calb (45.5%), LM (33.9%), HP (27.3%) and/or Asc (20.1%). The GIDs frequency was higher in older than younger children. The incidence of CD, LM and Asc was higher than in the general population. In ISS children with HP and Calb, IGF-I SDS values were significantly lower than in ISS children without GIDs.
Conclusions: High incidence of oligosymptomatic GIDs in short children both with ISS and GHD shows the need of thinking of gastrointestinal reason for short stature.
It should be recommended to make some tests and procedures for differential diagnoses of GIDs in the searching the causes of children short stature. The diagnostic tool should include: blood sample for antitransglutaminase immunoglobulin A antibodies, anti-HP antibodies, fecal Acaris eggs test or/and serologic anti-Asc antibodies, hydrogen breath test and stool sample for occult blood test and calprotectin concentration.

P3-d2-1371 Growth 8

Racial/ethnic differences in perceived barriers to short stature evaluation and treatment

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Background: Racial/ethnic disparities have been described among children receiving growth hormone treatment and specialist evaluation for short stature.
Objective and hypotheses: To examine parents' perceptions of barriers to the evaluation and treatment of short stature.
Methods: Parents of randomly selected children of any height, aged 9-14 yrs, from 9 primary care pediatric offices participated in 13 open focus groups (40 black, 31 white) and 10 nominal group technique sessions (24 black, 39 white). Based on parents' responses, a list of 10 potential barriers was incorporated into a one-time survey, which was then completed by other parents of children of any height, while awaiting their children's clinic visit at 4 primary care pediatric offices
(2 urban & 2 non-urban) during summer 2012. Parents rated their perceptions of the barriers on a 5-point Likert scale. Respondent race/ethnicity was modeled against the 10 barriers by nominal logistic regression analysis.
Results: 1820 surveys were completed (85% response rate; 1587 female, 231 male). Surveys with all barriers rated the same (n=194) were excluded as potentially unreliable. Barriers significantly
(P< 0.0005) associated with respondent race/ethnicity on logistic regression were: "regular doctor or nurse is not concerned about the height," "parent believes we should not interfere with God's will," "child may be treated differently if they were a boy or a girl," and "child may be treated differently based on their race or ethnicity." More white parents agreed with lack of clinician concern and child gender as potential barriers, while more black parents agreed that parents would not want to interfere with God's will. More Asian, black and self-described "other" parents saw child race/ethnicity as a potential barrier.
Conclusions: Understanding racial/ethnic differences in perceived barriers to the evaluation and treatment of short stature is an important first step in addressing disparities.

P3-d2-1372 Growth 8

Clinical, biochemical and radiological manifestations of newborns with hypocalcaemia due to vitamin D deficiency

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Background: Clinical features of neonatal rickets are not well described in the literature
Objective: To describe the clinical, biochemical and radiological manifestations of 10 full-term (FT) newborns presented to with symptomatic hypocalcemia (seizure) secondary to vitamin D deficiency (VDD) during the first week of life.
Methods: 10 newborns were studied. All were exclusively breast fed since birth. Their mothers had low 25 hydroxy vitamin D (25OHD) leve < 10 ng/ml and were dressed in their cultural customs, where most of the body was covered. Mothers were not taking vitamin supplements during pregnancy.
Results: Full-term newborns with hypocalcemia secondary to VDD had significantly shorter gestational age compared to controls. Their birth weight (2.84 ± 0.49 kg) and birth length (48.4 ± 2 cm) were significantly decreased compared to normal FT newborns. Generalized convulsions were identified by the medical staff. 8/10 had Craniotabes but none had rachitic chest rosaries or joint broadening. Physical as well as neurological examinations were within normal limits. Magnetic resonance imaging of the brain was normal. Hypocalcemic VDD newborns had serum 25OHD concentrations = 9.8 ± 1 ng/ml and their mothers had 25OHD concentrations = 9.1 ±1.5 ng/ml. 6/10 patients had increased PTH concentrations (> 60 ng/ml) and 6/10 had decreased magnesium concentrations (< 0.7 mmol/L). Their serum ALP concentrations were significantly higher than normal newborns. All other laboratory results (liver function, electrolytes, CRP, lumbar puncture, blood culture) were normal. Newborns with VDD had significantly lower serum calcium, ALP and PTH and higher PO4 concentrations, compared to older infants with VDD rickets. All newborn patients with VDD were started on alphacalcidol and calcium supplements and seizures ceased within two days of starting treatment.
Conclusions: Newborns are less adapted to VDD. This explains their different clinical presentations.

P3-d2-1373 Growth 8

12q subtelomere deletion in a child with delayed psychomotor development, food seeking behavior, obesity, growth retardation and congenital heart defect

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Background: 12q subtelomere deletion is a rare genomic condition with a variable nonspecific phenotype. Here, we report on an additional 12q subtelomere deletion in a child diagnosed by array comparative genomic hybridization (aCGH).
Objective and hypotheses: We saw a 5 year old girl born at term, sectio because of threatening asphyxia, apgar 10/1 BW 3170 g, BL 49 cm, head circumference 35 cm. The girl had mild delayed psykomotor development, growth retardation (length -3 SD), obesity (Weight -0,5 SD) and congenital heart defects (ASD and VSD). She had multiple episodes of otitis media and failure to thrive during the first years of life. Behavioral problems included food-seeking behavior, hyperactivity, and high pain threshold. Dysmorphic features were frontal bossing, small ears with preauricular fistulas, high palate, mild webbed neck, widely spaced nipples, lipodystrophy and mild clinodactyly. Further she had a stocky building. Turner and Prader-Willi Syndrome were suspected.
Methods and results: Genetic studies demonstrated a normal karyotype 46XX (Q-banded karyotype) and a normal FISH-analysis for Turner Syndrome. High resolution aCGH applying Agilent 180K oligo array including parental analysis revealed a de novo 4,7 Mb subtelomere deletion at chromosome 12q24.32q24.33. Further we found IGF 1 < -2SDS, arginine provocative test revealed peak growth hormone 9,49 mU/L, and clonidine provocative test will be performed.
Conclusions: Our patient had similar clinical phenotype as earlier reported including mild delayed psykomotor development, growth retardation, mild dysmorphic features and behavioral manifestations as food seeking behavior. Furthermore, our patient had congenital heart defects. This report further delineates the 12q subtelomere deletion syndrome and illustrates the importance of aCGH as first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies.

P3-d2-1374 Growth 8

Linear growth after paediatric liver transplantation

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Background: Chronic and severe liver diseases adversely affect linear growth. The magnitude of this growth retardation and the effect of liver transplantation on growth is scarcely studied.
Objective and hypotheses: To determine growth patterns in a children undergoing liver transplantation.
Methods: The outcomes of orthotopic liver transplantations performed in 10 children at Hamad General Hospital between October 2005 and October 2009 were reviewed.
Results: The mean age at transplantation was 27 ±30 months; 80% of the children were females. The transplants were from living-related donors. At the time of transplantation the mean height z score was - 1.15 ±1.7 and BMI z score was 0.44 ±1.8. Eighteen months after transplantation, catch-up growth was seen in 40% of children, 30 % had normal linear growth without any catch-up and 30% had slow growth rate after transplantation. Children with evidence of catch-up growth (growth velocity z score >0) had more growth retardation at the time of transplantation, and were receiving lower doses of prednisone at 1.5 years after transplantation. Younger infants (below 6 months) were most likely to demonstrate catch-up growth after transplantation. In summary, a large proportion of children have growth retardation at the time of liver transplantation. Serum albumin increased significantly after (39.8±5.2 g/L) vs before (34 ±11g/L)transplantation, and Alanine transferase (ALT) decreased significantly from (130±260U/L) to (30±15U/L). Poor growth after transplantation occurred more in those receiving higher doses of corticosteroid. Growth after transplantation is proportional to the degree of growth retardation at transplantation and inversely correlated to age at transplantation.
Conclusions: 40 % of children had catch-up growth after LT while 30% maintained normal growth without CU. Poor growth after LT occurred more in those receiving higher doses of corticosteroid.

P3-d2-1375 Growth 8

Three years of growth hormone therapy in children with growth deficiency

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Background: Growth hormone (GH) therapy improves height outcome in children with growth hormone deficiency (GHD). Height velocity (HV) is maximum in the first year of treatment. Early diagnosis and therapy initiation optimize growth outcomes.
Objectives: To evaluate growth and safety during the first 3 years of GH treatment in 33 GHD children.
Methods: 33 prepubertal children (23 boys, 10 girls) were included: IGHD (isolated GH deficiency)=30, MPHD (multiple pituitary hormone deficiency)=3. All of them were treated with a mean dose of GH=0.035mg/kg/d and followed for at least 3 years (mean 4.98ys).
Results: The mean height standard deviation score (SDS) increased from -2.76 at baseline to -1.14 at 3 years; the change in height SDS decreased with time.

Parameter	Baseline	1year	2years	3years
Chronological age(ys)	7.89	8.89	9.89	10.89
Bone age(ys)	5.76	6.62	7.44	9.46
IGF-1 mean values (ng/ml)	64.64	221.8	205.7	265
Height SDS	-2.76	-2.12	-1.55	-1.14
Height velocity(cm/yr)	-	10.59	7.48	6.04
Weight SDS	-1.94	-1.28	-0.94	-0.46

[Table 1: Growth data during first 3 years of GH therapy in 33 GHD children.]

Within first 3 years of therapy none of these children developed diabetes mellitus, 6 patients (18.18%) presented transient increase in fasting glucose (>100 <126mg/dl), 1 patient (3.03%) had transiently impaired glucose tolerance (<140 <200mg/dl at OGTT), 1 patient (3,03%) developed hypothyroidism and 3 patients (9.09%) had transiently increased TSH levels (normal fT4 values,no clinical signs). No malignancies were observed to date.
Conclusions: GH treatment significantly improves growth of GHD children, with a favorable safety profile. The maximum height velocity was observed in the first year of therapy (10.59cm/yr); the second and the third year of treatment resulted in a lower height velocity (7.48cm/yr respectively 6.04cm/yr). No severe adverse events were observed.

P3-d2-1376 Growth 8

Etiologic analysis of 1023 children with short stature in Shanghai, China

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Objective and hypotheses: The definition of short stature is a height more than 2 standard deviations below the mean for age and gender, or below the third percentile. The causes of short stature are complicated, so the diagnosis are very important. We analysis the etiologic investigation of 1023 children in Shanghai China with short stature to find out the diagnostic flow of short stature initially, to provide a worthy reference of diagnosis, treatment and prevention for those type of short stature.
Methods: 1023 children were collected, among them 611 were males (59.73%), 412 were females (40.27%),the average age was (12.24±5.51) years. All of the children were collected detail medical history and taken both physical and laboratory examination.
Results: 22.23% was diagnosed as growth hormone deficiency (GHD), 19.64% was diagnosed as constitutional delay of growth and puberty, 15.82% was diagnosed as familial short stature, 17.25% was diagnosed as idiopathic short stature. The rest of the short statures were attribute for the other reasons and some are very rare.
Conclusions: Endocrinopathy can cause short stature. GHD is a common disease among them. Some hypothyroidism has not special countenance and has no difference in intelligence development from others, so the investigation of thyroid function is important for these children. For short stature children, correct treatment is according to the pathogens. After an assessment of short stature has been made, appropriate therapy may be instituted.

P3-d2-1377 Growth 8

Can only local IGF-I hold normal growth during pubertal spurt?

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Introduction: Final stature is a result of concomitant GH-IGF-I axis integrity, a healthy environment and genetic background. Occasionally, growth occurs despite remarkable impairment in hormone profile.
Case study: We report on the case of a 19 year-old male patient with the diagnosis of osteopetrosis who had a falloff in growth at the age of 14 years, Tanner G1P1, but recovered height gain velocity months latter, suggesting a prepubertal slowdown in growth. However, his IGF-I concentrations were consistently low (< -2 SDS). Two GH provocative tests were performed and resulted in appropriated cortisol release, but there was no response of GH to the stimulus. Low to normal LH and FSH levels, low testosterone concentrations and Tanner stage G3P3 at age of 19 years suggested partial hypogonadism. A third provocative GH test was then performed after testosterone replacement. Despite this stimulus GH was undetectable at all samples. Lumbar spine bone mass was increased (z-score= +5.1) and there were calcifications within the skull base but normal brain MRI. At age of 16 years he had a femural fracture with abnormal consolidation, leading to walking limitation. His final height is 179 cm (0.43 SDS), above familial target height.
Conclusion: This original case report describes a patient harboring osteopetrosis, a disease usually associated with short stature and normal GH/IGF-I axis. Curiously, the patient exhibited normal height development in spite of GH deficiency. Further studies are necessary to evaluate the role of growth factors production and action on bone microenvironment in this condition.

P3-d2-1378 Growth 8

Childhood growth in female patients with congenital hypogonadotropic hypogonadism

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Background: Congenital hypogonadotropic hypogonadism (CHH) provides a model to study the contribution of sex steroids during different phases of growth. Herein, we report the pattern of growth throughout childhood in six females with CHH.
Objective and hypotheses: To describe childhood growth in females with CHH.
Methods: We describe growth patterns throughout childhood in six females (5 with heterozygous *FGFR1* mutation [one mother-daughter pair] and one with biallelic *GNRHR* mutations). All had severe gonadotropin deficiency.
Results: In all patients, length at birth was within ± 2 SDS. During childhood, growth started to decelerate at a mean age of 7.7 yrs (range 4-10 yrs). Only one patient with an *FGFR1* mutation displayed slightly elevated body mass index between 15 and 17 yrs of age.
Conclusions: Girls with CHH displayed slight deceleration of growth already before the expected age of puberty onset. Although *FGFR1* is associated to obesity at population level, female *FGFR1* mutation carriers were not obese during childhood.

P3-d2-1379 Growth 8

Primary hypertrophic arthritis in differential diagnosis of acromegaly - case report

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Background: Assessment of any child who is unusually tall or presented the characteristic features of acromegaly must consider pathologic causes of excessive growth hormone concentration in blood.
Objective and hypotheses: Almost 18-year-old boy who was admitted to our Department of Endocrinology with suspected acromegaly. In a history patient demonstrated enlargement of knees, wrists, ankles circumferences, without redness or pain, but with hyperhidrosis and simultaneously acceleration of growth. Since October 2010 patient remained under rheumatological medical care in local hospital, where juvenile idiopathic arthritis was diagnosed and started therapy of methotrexat without any improvement. On admission to our Clinic patient was in good condition, physical examination revealed excessively long limbs, enlargement of knees, ankles, wrists circumferences, large hands and feet, hyperhidrosis.
Methods: Endocrine, imaging studies and genetic consultation.
Results: Hormonal test showed normal levels of androgens, IGF-1, growth hormone in glucose suppression test. MRI of central nervous system and bone scintigraphy appeared to be normal. During genetics consultation primary hypertrophic arthritis has been diagnosed. Currently there is no capacity to

perform the diagnosis adequate genetic testing.
Conclusions: In the differential diagnosis of acromegaly we should consider rare disorders like primary hypertrophic arthritis.

P3-d2-1380 Growth 8

Distinctive craniofacial features associated to cone-shaped epiphyses at the phalanges and short stature: trichorhinophangeal syndrome, type I

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Background: Trichorhinophangeal syndrome, type I is a rare genetic condition caused by mutations in the gene *TRPS1*. It is characterized by distinctive craniofacial features and skeletal abnormalities, including short stature.
Objective and hypotheses: To report the clinical features of a patient with trichorhinophangeal syndrome, type I, calling attention for the findings that lead to its diagnosis.
Population and/or methods: We performed the description of the case with a literature review.
Results: The patient was a girl of 8 years of age with history of growth retardation and delayed bone age. There were no similar cases described in the family. The patient was born vaginally at term, measuring 48 cm, weighing 2740 grams, with a head circumference of 33 cm. She was born with an umbilical hernia that was surgically corrected at 3 years of age. Short stature was noted at age 8. She evolved with appropriate developmental milestones. She had no cognitive impairment. Her hormone levels were normal. At dysmorphological examination, at 8 years of age, we observed short stature (119 cm), sparse hair, pear-shaped nose, prominent ears and ligamentous laxity. There was no development of breast or pubic hair. Radiographic evaluation showed the presence of cone-shaped epiphyses at phalanges; thinning of the shafts of the long bones of the arms and legs; shortening of metacarpals and metatarsals and lesion in the distal femur suggestive of non-ossifying fibroma. The patient's karyotype was normal.
Conclusions: The clinical and radiological findings observed in our patient were consistent with the diagnosis of trichorhinophangeal syndrome, type I. This diagnosis should be considered in patients with short stature associated to cone-shaped epiphyses. Furthermore, it is important to remember that the syndrome is an autosomal dominant condition, i.e., there is a risk of 50% of future disease transmission to offspring of the patient.

P3-d2-1381 Growth 8

A case of Crouzon syndrome associated to growth hormone deficiency

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Background: M. is a 8 years and 11 months old boy who came to our attention for short stature.
Objective and hypotheses: Since the age of two years, M. showed dysmorphic craniofacial features such as brachycephaly, severe ocular proptosis with hypertelorism, hypoplasia maxilla with relative prognathism, arched palate, parrot-beak nose and sindattilia. At the age of 4 years, he was diagnosed with Crouzon Syndrome.
Method: To evaluate the presence of mutations in the well-known genes involved in the syndrome, molecular analysis was performed. It showed absence of mutations.
Results: On auxological evaluation, M. presented a marked growth retardation. Stature was 118 cm (< 3°centile, -2,1DS), growth rate 4 cm/year (< 25°centile). Genetic target was 173,3 cm (-0,2 DS). The radiograph of the wrist and hand showed a bone age of 5 years. Blood examination was performed: complete blood count, electrolytes, ferritin, screening for celiac disease, evaluation of thyroid function, urinalysis. The results were normal. IGF1evaluation (< -2 DS) and stimulation tests for growth hormone (< 10 ng/dl) showed patological values so M. was diagnosed with growth hormone deficiency. Brain MRI showed adenohypophysis hypoplasia.M. started growth hormone therapy at a dose of 4,3 mg/week. After the first year of therapy, at the chronological age of 10 years, the stature was of 126 cm (5°centile, -1,7 DS) and growth rate was 7 cm/year (97°centile).
Conclusions: At present, whole genetic causes responsible for this syndrome aren't known and 30-60% of these patients have a de novo mutation.
Children with Crouzon Syndrome should be monitored closely for all growth parameters, not just head circumference. In these patients is important to evaluate pituitary function. In literature, only 2 case of Crouzon Syndrome and growth hormone deficiency are reported.This case shows the potential efficacy of growth hormone replacement therapy in patients with Crouzon syndrome and growth hormone deficiency.

P3-d2-1382 Growth 8

The effect of social environment on height and sexualisation process

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Background: Influence of bio-psycho-social environment on some features auxological is certain.
Objective and hypotheses: Assessment of anthropometric (height, weight) and biological (menarche age) characteristics for school age children 11-14 years of diverse backgrounds.
Methods: We studied 1803 children (543 boys and 1260 girls) from different backgrounds and schools (4), appreciating the financial status of the family, psycho-emotional environment, social behavior, correlations were made with somatic development and menarche appearance in girls of pubertal age. Data were assessed by Romanian Standards for Age and Sex.
Results: The medium height and weight of children coming from school no. 1, 2, 3 were within normal limits (according to Romanian standards for age and sex). The values of the children from school no. 1 were superior to the ones from schools no.2 and 3. The medium height and weight of children coming from school no. 4 were beneath inferior normal limits (according to Romanian standards for age and sex). The lowest value for the medium menarche age obtained for the girls was for school no.1: 11.1±0.94 years and the highest age was found in the girls from school no. 4: 13.4±1.13 years. In girls from schools no. 2 and 3 the values were: 11.8±1.24 years, respectively 12.7±0.62 years.
Conclusions: Inadequate psycho-social factor represents a possible disturbing element in psycho-somatic development of children, but the age of onset of menarche is less influenced.

P3-d3-1383 Growth 9

Long-term follow-up of a case with a clinically recognizable genetic cause of short stature-KBG syndrome

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Introduction: KBG syndrome is a possibly underdiagnosed disorder characterized by macrodontia of the upper central incisors, minor facial dysmorphisms, skeletal anomalies, global developmental delay, and short stature (mean final height: female, 149 cm, male, 153.6 cm). The genetic cause was not evident until 2011, when *ANKRD11* mutations have been established in half of the cases.
Case study: The patient, who was receiving special education due to mild mental retardation, was first admitted at the age of 12.5 years. She was born to non-consanguineous parents [mother 160 cm, father 174 cm, target height

160 cm (SD score -0.44)]. Physical examination revealed a height of 133 cm (SD score -2.96), weight 24.4 kg (SD score -3.81), triangular face, synophrys, bulbous nose, clinodactyly, and Tanner stage II breast development. Investigations disclosed normal biochemistry, bone age consistent with 10.5-11 years, and peak growth hormone levels of 5.4 ng/mL and 5.8 ng/mL with insulin-tolerance and L-Dopa growth hormone stimulation tests, respectively. Growth hormone treatment (0.2 mg/kg/week) was initiated. During the follow-up, macrodontia of the upper central incisors (10 mm wide, normal < 9.7 mm) was noted and KBG syndrome was considered. At the age of 17 years, growth hormone treatment was stopped since the epiphyses were partially fused (near-final height, 151.6 cm, SDS -1.74). Demonstration of two *de novo* novel heterozygous mutations in *ANKRD11* (c.1785G>T and c.1786C>T) confirmed the diagnosis.
Conclusion: Macrodontia should be looked for during evaluation of short stature. Growth hormone treatment did not appear to be of major benefit in the case.

P3-d3-1384 Growth 9

Turner syndrome: results after three years of growth hormone therapy

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Background: Adult height of patients with Turner syndrome (TS) is 20cm shorter than in general population. Growth hormone (GH) therapy improves height outcome in girls with TS; results depend on age at diagnosis, duration of therapy and doses of GH.
Objectives: To evaluate growth and safety during the first 3 years of GH treatment in patients with TS.
Methods: Eight prepubertal girls with TS were included, mean age of 11.54ys. They were treated with a mean dose of GH=0.037mg/kg/d and followed for at least 3 years (mean 4.2ys).
Results: The mean height SDS score increased from -3.61 at baseline to -1.92 at 3 ys. Main gain over 3 ys was 19.5cm. The mean weight SDS score increased from -1.28 at baseline to -0.80 at 3 ys. Bone age was delayed at diagnosis by a mean value of 1.17 ys and after 3ys the delay decreased to 0.29ys (Table 1).

Parameter	Baseline	1year	2years	3years
Age (ys)	11.54	12.54	13.54	14.54
Bone age (ys)	10.37	10.95	12.48	14.05
Height SDS	-3.61	-3.05	-2.48	-1.92
Height velocity(cm/yr)	-	8.53	6.85	4.11
Weight SDS	-1.28	-1.08	-0.86	-0.80

[Table 1]

Safety profile: There were no cases of diabetes mellitus, impaired glucose tolerance or malignancies; four patients had transient increase in fasting glucose(>100< 126mg/dl); one patient developed hypothyroidism.
Conclusions: GH treatment is associated with highly significant changes in growth. In our study height velocity was maximum (8.53cm/yr) in the first year of GH treament; the improvements in growth declined in the second (6.85cm/yr) and third year (4.11cm/yr). GH therapy had a favorable safety profile. Delayed diagnosis of TS has a negative impact on growth outcomes.

P3-d3-1385 Growth 9

Growth hormone treatment in an active paediatric Crohn's disease

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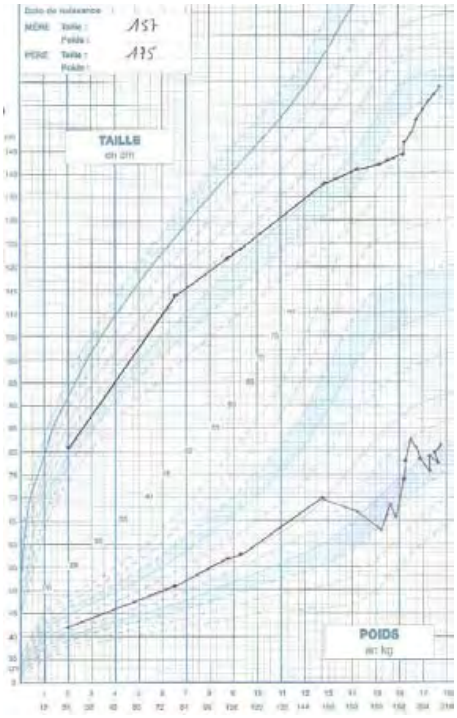
Background: Crohn's disease is a chronic inflammatory disorder of the bowel. Failure to thrive is present at diagnostic on children, and is often persistent into adulthood, leading to short stature. Three previous studies have demonstrated the benefits of the Growth Hormone (GH) therapy in Crohn's disease.
Case report: Hereafter we will introduce a boy who presented at 15years and 4 months old for failure to thrive. His height was at -4DS and his weight at -3DS. He was born Small for Gestational Age. He was suffering from abdominal pains and diarrhea. Antisaccharomyces cerevisiae antibodies were positive and colonoscopy has confirmed Crohn's disease. At the same time, somatotropic exploration has shown a deficiency with IGF1< -2DS, and GH < 10UI/l at glucagon betaxolol test. The first month, he was treated with corticosteroids. Throughout the period, he continued to take enteral nutrition, mesalazine, aziathropine and a multiple vitamin. It was associated with growth hormone therapy, administrated daily, at 0.05 mg/kg/j. After 29 months of GH, he was in clinical remission. His height had increased 17 cm: height was-2.5DS and weight -2DS. Puberty started spontaneous at 16 years and 3 months.IGF1 levels were within normal range for Tanner stage



[Curve of growth]

Conclusions: This original observation shows that association GH therapy may increase height velocity in Crohn's disease. Further study is necessary to determine the role and the way in which growth hormone may benefit patients with Crohn's disease.

P3-d3-1386 Growth 9

Celiac disease and GH deficiency: report of two cases

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Introduction: Celiac disease (CD) is a genetically determined, autoimmune, chronic inflammatory state caused by intolerance to gluten. In some patients, short stature may be the presenting symptom, making the diagnosis of CD challenging. Rarely, it has been shown that poor catch-up growth after gluten-free diet may be due to the coexistence of CD and GH deficiency.
Case study: We present two children with coexisting CD and GH deficiency who increased linear growth after GH replacement therapy. Patient 1: a girl referred for short stature at the chronological age (CA) of 7 yrs: height was 108.2 cm (- 2SD), target height 10°-50°, bone age (BA) was 4 yrs. Duodenal biopsy confirmed CD diagnosis and the girl started a gluten-free diet. After 3 years of gluten-free diet linear growth was still poor. Evaluation of GH secretion (insulin and clonidine stimulation tests) that was delayed until the CA of 11.9 yrs showed GHD: height was130 cm (-2.2 SD). After 1 year on GH therapy (1.4 mg/die) the patient started pubertal development: treatment with LHRH analogue was associated to GH until the CA of 14.2 yrs. At the last clinical examination, CA was 15.5 yrs, height 153.5 cm (3°-10° ct), BA 10.5 yrs.
Patient 2: a boy diagnosed with CD at the CA of 6.5 yrs. At a CA of 10.9 yrs he was referred for short stature: height was 128.5 (-2.2 SD), (target height 3°-10°), BA was 10 yrs. Evaluation of GH secretion (insulin and clonidine stimulation tests) revealed GHD and GH replacement therapy (1 mg/die) was started. At 12.9 yrs, after 2 years on GH therapy, the patient began pubertal development: height was 143.5 cm (3°-10° ct), BA 12.5 yrs. At the last clinical evaluation, CA was 13.2 yrs,
height 146.5 cm (10° ct), pubertal development Tanner stage 2.
Conclusion: GH secretion should be evaluated in CD patients showing no catch-up growth after a gluten-free diet. GH therapy associated with gluten-free diet led to an increased growth rate.

P3-d3-1387 Growth 9

Rare genetic mutations in patients with dwarfism

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Introduction: We would like to report two cases of severe short stature, where the final diagnosis was established after molecular genetic testing. Both patients had a rare association of severe short stature and bone marrow involvement with a genetic basis for their condition.
Case studies: The first patient presented with pre and postnatal growth retardation, birth weight of 1.2 kg at 34 weeks gestation. She remained proportionately small. Pericentrin gene mutation was requested in view of her phenotype suggestive of Osteodysplastic Primordial Dwarfism, but this was negative. Growth hormone treatment was initiated under "small for gestational age" licence. During this treatment, she developed thrombocytopenia, with a hypocellular bone marrow. Growth hormone was discontinued. Genetic testing for LIG 4 gene mutation confirmed two separate mutations, which explained the association of her problems. Additional features of DNA Ligase IV syndrome include immune deficiency, developmental delay and radio-sensitivity.
The second patient was small for gestational age, with a birth weight of 1.4 kg at 32 weeks gestation. At 3 years of age he was extremely short, with a relatively large head and a prominent forehead. His growth faltered further with development of immune deficiency and pancreatic exocrine insufficiency. Genetic testing confirmed Cartilage-Hair Hypoplasia (RMRP mutation) with associated combined immunodeficiency, for which he underwent bone marrow transplantation at 10 years of age. He remains well post transplant, currently on growth hormone treatment which appears to be promoting his growth.
Conclusion: In both patients, the aetiology of extreme short stature was secured when new clinical features appeared, leading to specific genetic testing. Both these conditions are inherited in an autosomal recessive pattern. There is no associated endocrinopathy with either of them, however, both patients received growth hormone therapy with some response.

P3-d3-1388 Growth 9

Abstract has been withdrawn

P3-d3-1389 Growth 9

Saizen®-online: a longitudinal observational study on the efficacy and safety of recombinant human growth hormone for paediatric indications

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Background: Growth Hormone (GH) Deficiency (GHD), Small for Gestational Age (SGA), Turner Syndrome (TS) and Chronic Renal Insufficiency (CRI) require long-term GH supplementation. Saizen® is a recombinant human GH (r-hGH), approved in many countries worldwide for these indications.
Objective: The aim of this longitudinal non-interventional study is to collect efficacy and safety data on the long-term pediatric use of r-hGH under everyday conditions.
Population and methods: This is a multi-centric, longitudinal, prospective, non-interventional study in pediatric patients with GHD, TS, SGA and prepubertal CRI that receive r-hGH supplementation. Planned observation period is 15 years with a recruitment period from 2007 until 2016. Data such as demographics, height, laboratory parameters and adverse events are recorded on standardized forms. Additionally, adherence data are collected by the patients with easypod™. Easypod™ is the only hidden-needle auto-injector device for growth hormone (Saizen®) delivery which accurately records dose and injection time.
Results: Descriptive interim analysis of 1401 evaluable patients who were treated over an average of 3 years is presented for the period 2007-2012. The majority of patients suffer from GHD, followed by SGA, TS and CRI. Growth rate is presented as change of standard deviation score (SDS) and the achieved growth indicates good efficacy of the r-hGH therapy across all indications. The overall good tolerability indicates a good safety profile of Saizen®.
Conclusions: Long-term treatment with r-hGH increases growth rate in pediatric patients with GHD, TS, SGA and CRI and is tolerated well. As treatment effects are more pronounced in younger children, continuous r-hGH supplementation therapy should be initiated as early as possible.

P3-d3-1390 Growth 9

Acute myocardial infarction in a male adolescent receiving the aromatase inhibitor anastrozole: is there a causal relationship?

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Background: Previous reports of a significant elevation of both hemoglobin and testosterone levels in adolescents receiving aromatase inhibitor (Ais) and of thrombo-embolic events in adult women using Ais for breast cancer treatment, raise concerns of possible deleterious cardiovascular effects of Ais in adolescents male being treated in an attempt to increase their final height.
Objective and method: This report describes a severe cardiovascular event in a 14 year old pubertal male (Tanner stage V) with idiopathic short stature (height: 154 cm, bone age: 13.6 years, midparental height: 170.5 cm) who received the third generation Ais, anastrozole (1 mg/d for 4 months before the event) prescribed in order to delay skeletal maturation and extend the available time for linear growth.
Results: He presented with typical severe retrosternal pain radiating to the left arm, electrocardiogram ST elevation of more than 1 mm in the lateral leads and elevation in the creatinine kinase MB fraction (21 U/L) and troponin I levels (14.1 ng/ml). Hemoglobin and testosterone levels were: 15.5 g/dl

and 11.1 ng/ml. Calcium channel blocker therapy was initiated with no recurrence of anginal chest pain on follow-up. Ais was immediately suspended. No congenital coronary and cardiac anomalies or coronary thrombi were detected by echocardiography. Heart catheterization and coronary angiography excluded atherosclerotic and thrombotic processes and also suggested a vasoactive mechanism. Laboratory evaluations for hyperlipidemia, drug abuse or hypercoagulability were negative.
Conclusions: Whether Ais therapy played a causative role in the acute myocardial infarction of this child remains unclear. However, the complex interplay between the endocrine actions of androgens and the paracrine actions of myocardial produced estrogens on the cardiovascular system raise safety questions on Ais use in male adolescents.

P3-d3-1391 Growth 9

AEG syndrome (syndromic microphtalmia type 3): endocrine involvement in a patient with a new mutation

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Background: AEG syndrome is an AD MCA/MR caused by mutations/deletions in SOX2 gene.
Objective and hypotheses: We describe a pt with MCA/MR, GH deficit (GHD) and hypogonadotropic hypogonadism (HH).
Method: 2nd child of healthy non consanguineous parents. Negative family history. Born at term after caesarean section, pregnancy with poliidramnios. Birth weight 2.75 kg, length 47 cm. At the birth bilateral anophtalmia, micropenis, cryptorchidism and esophageal atresia type III (surgically repaired at 8 mts). MRI: cavum septi pellucidi, anophtalmia, optic nerve and corpus callosum hypoplasia; normal pituitary gland. Normal kidneys and heart. Clinical evaluation: blepharofimosys, anopthalmia, large ears, small hand, terminal hypoplastic fingers, dorsal lymphedema of feet, cleft scrotum, cryptorchidism, micropenis, truncal hypotonia. In the follow-up: MR and short stature (H< 3rd centile).
Results: GHD was diagnosed and treated with GH therapy. Gonadal function showed HH treated with testosterone therapy. No other endocrine involvement. At 18 yrs: stature (near final height): 158.2 cm (< 3rd centile), weight 47.1 kg (25th centile for height age), OCF 50 cm (< 3rd centile), PH 4 and T 4 ml. BA 16.5 yrs.
Normal CGH array. At SOX2 analysis: new mutation c.166deC (p.Arg56Glyfs*47).
Conclusions: AEG syndrome is characterized by anophtalmia or microphtalmia with or without defects of the optic nerve, chiasm and optic tract, brain anomalies, seizures, neurocognitive and motor delays, hearing loss and esophageal atresia. Hypoplasia of anterior pituitary is another major complication, wich frequently results in GHD; HH is the most consistent endocrinopathy in SOX2 mutation and . SOX2 gene is also involved in isolated HH. In our pt GHD is not associated with anterior pituitary hypoplasia. HH is constant in SOX2 mutations and GHD could be investigated also in pts with normal pituitary gland. GH therapy improves final height but in our pt near final height remained < 3rd centile.

P3-d3-1392 Growth 9

Growth and puberty abnormalities in a 15-year old boy with partial chromosome 15q26.2-qter trisomy coding gene of IGF1 receptor and chromosome 21p-21q21.2 trisomy excluding Down syndrome critical region - case report

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15-year old boy with chromosome aberration: 47,XY,+der(21),t(15;21)(q26.2;q21.2)pat, severe mental retardation, epilepsy, hypothyroidism and growth disturbance. So far identical clinical phenotype with this particular mutation hasn't been reported.
The boy was born as a result of XI pregnacy, IX delivery (there were 2 miscarriages) in 37 week of pregnacy with body weight of 4200g, length of 57cm, 6 points Apgar score. Since first year of life boy has been treated with valproic acid with good results. In 13th year of life abnormalities of behaviour started to intensify and gradual regress of aquired capabilities appeared. Brain CT (3ys of age) and MRI scan (8ys of age) were normal. MRI scan done at the age of 13 showed cortex and cerebellar vermis atrophy.
Boy has been treated with L-thyroxine since the age of 11 with good results. Until 12 ys height was > 97c, since then delay of growth velocity (8 cm/year to 2,6cm/year) and puberty (LH/FSH 3,1; testosterone < 20ng/dl; testis volume 4ml) has been observed.
Phenotype: Flat face profile, longitudinal face, prominent frontal eminences, sparse eyebrows, ptosis, enlarged mandible, partial syndactyly of finger 3 and 4, dysproportion between torso and extremities length.
Conclusions: Patomechanism of these abnormalities is complex and is a result of chromosomal aberrations. Mental retardation and growth abnormalities might be an effect of overexpression of the genes located on the extra copy of chromosome 15q26.2-qter,where IGF1 receptor gene is located (15q26.3 locus). Intelectual isufficiency, hypothyreosis, lack of the Down syndrome characteristic features are the effect of presence of an extra copy of 21p-21q21.2 chromosome excluding critical region of Down Syndrome 21q22.3. Molecular analysis is still in progress.

P3-d3-1393 Growth 9

Subjective global assessment of hospitalized children

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Background: Nutritional assessment of children in the first days of hospitalization has a fundamental importance; and, the use of subjective parameters in clinical practice is a simple method, considered an low-cost instrument, noninvasive, which can be performed at the bedside.
Objective and hypotheses: The objective of this study was to evaluate hospitalized children from 2 to 10 years using a nutritional subjective assessment and incorporated this instrument in the nutritional screening of these pediatrics patients.
Methods: The questionnaire was used typically required to meet the nutritional profile of the children and that affect the result of nutritional assessment. The questionnaire was called Subjective Global Assessment in Hospitalized Children (SGAHC). The variables used in the questions are: birth weight, gestational weeks, breastfeeding, food allergies, gastrointestinal symptoms, number of previous admissions and number of meals that the child has each day. According to the score, the patient was classified as "With Nutritional Risk" and "Without Nutritional Risk".
Results: Of the 45 children evaluated, 37 (82%) were without nutritional risk and 8 (18%) were at nutritional risk. Among the questions that comprise the record, those that were stressed showed more changes, were: birth weight, while 44 (98%) had normal weight and 1 (2%) were underweight at birth; relation to breastfeeding, where 43 (96%) were breast-fed and 2 (4%) were not breastfed; what about the introduction of complementary food, from the children who started breastfeeding within only 25 (56%) mothers received professional guidance for introduction of other foods and 20 (44%) did not.
Conclusions: The preparation of this statement follows an assessment tool in a simple and easy application by the interdisciplinary group, allowing early nutritional management of hospitalized children. The use of SGAHC is a very practical procedure for observe the nutritional risk.

P3-d3-1394 Growth 9

An unusual same karyotype anomaly in a mother and her two daughters with short stature: 46, X, del(x)(p21 pter)

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Introduction: Infertility and short stature are the most common features of Turner syndrome.
Case study: Here we reported a mother and her two daughters with 46, X, del(x)(p21 pter). Our first patient was older daughter, 9-year-old and she admitted to outpatient clinic for short stature. Her pubertal staging was Tanner stage 2. Her FSH and LH were normal for pubertal stage. Karyotype analysis showed 46, X, del(x)(p21 pter). After that her mother and younger sister has been evaluated and observed that mother and sister had short stature and same karyotype.
Conclusion: We recommend that karyotype analysis must be mad efor evaluation of short stature even if the patient has no Turner syndrome properties. Also we want to point that patients with Turner syndrome with 46, X, del(x)(p21 pter) may be fertile.

P3-d3-1395 Growth 9

Achondroplasia: about thirteen patients

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Background: Ostéochondroplasies are pathologies in relation to alterations of genes involved in bone formation. Achondroplasia is the most common cause of genetic dwarfisms. It is an autosomal dominant disease associated with mutation of the receptor gene growth factor fibroblastesFGFR3. It is characterized by rhizomelic dwarfism and multiple complications.
Objective and hypotheses: Clarify the clinical features and search complications associated
Methods: Thirteen children with achondroplasia were hospitalized. In addition to a clinical examination a paraclinical was conducted involving skeletal radiographs, MRI brain and spine, a metabolic balance and a hormonal investigation: IGF1, TSHus, FT4, and glucagon test. In addition to the treatment of complications, a therapeutic trial with GHr was undertaken in 3 patients.
Results: The average age of children was 9 years ± 2 months(12 F, 1G)
The reason for consultation was delay stature. Rhizomelic dwarfism: -4.5 DS (-3, -6) and macrocrania were observed in all cases. 12 patients had obesity. Hypotonia is found in one case with spinal cord compression requiring neurosurgical cure. Syndrome Sleep apnea is found in a child who had a narrow nasal drawplate and vegetation.Deformities in the lower limbs and a psychological impact were observed in the older (5) Metabolic and hormonal balances were normal.A height gain (+1 SD) was observed in patients receiving GHR after a year of treatment.
Conclusions: The chondroplasie is easily recognized. Possibilities of neurological, bone, metabolic and psychological complications should encourage the search. The use of biosynthetic growth hormone has been trials and could be effective in some patients. Current treatment is mainly orthopedic. Heavy This is a technique that should be considered after the end of growth. research primarily target the inhibition of FGFR3 receptor . The development of these Therapeutic would effectively manage the disease and prevent its complications.

P3-d1-1396 Perinatal and Neonatal Endocrinology 3

Improved head and linear growth at 36 weeks in extremely preterm infants (< 27 weeks) with early intensified parenteral nutrition

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Background: Meeting nutritional needs of preterm infants represent a balance between growth and development of the infant and prevention of complications associated with parenteral nutrition.
Objective and hypotheses: To evaluate the effect of a new compounded parenteral nutrition with increased protein and energy content and new fat composition on growth in extremely preterm infants.
Methods: A retrospective, cohort study design was used. Infants born < 27 gestational weeks at Uppsala University Hospital, between 2009-09-01 and 2012-06-30, and who received partial parenteral nutrition for four days or more, were included. Data regarding the patients were collected from the Swedish National Perinatal Register (PNQ) and medical records. There were 48 infants in the intervention group who had received the new parenteral nutrition and 42 infants in the control group who had been given the older regimen.
Results: The median birth weight was 720 (340-976) and 732 (448 -1064) and gestational age was 25 weeks+1 days (22+0-26+6) and 25 weeks+2 days (22+0-26+6) in the intervention and control groups, respectively. Mean age at regained birth weight was 8,7±4,2 days in the intervention group and 11,5±4,0 days in the control group. Length and head circumference were greater at 36 weeks of gestation in the intervention group (length, p=0.015 and head circumference, p= 0.015). There were no difference between the groups in number of complications during the hospital stay. Infants born appropriate for gestational age in the intervention group had a decreased risk of being small for gestational age (< -2 SD) at 36 weeks (12,5% vs. 34%, p=0.024).
Conclusions: The extremely preterm infants seem to benefit from increased levels of protein and energy content in partial parenteral nutrition. The infants receiving more aggressive nutrition during their first days of life, regained birth weights earlier and had greater head circumference and length at 36 weeks of gestation.

P3-d1-1397 Perinatal and Neonatal Endocrinology 3

Transient abnormalities in brain MRI in a newborn with X-linked congenital adrenal hypoplasia

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Background: The hallmark of adrenal hypoplasia congenita (AHC) in the neonatal period is salt wasting syndrome and hypoglycemia. Transient abnormalities in brain MRI have not been reported so far to our knowledge in this entity. However they have been described in others diseases that usually have hypoglycemia and electrolyte imbalances.
Objective and hypotheses: To report a newborn with AHC and transient brain hyperintensity in MRI.
Methods: Case report
Results: At 3-days-old male was admitted in the neonatology unit because of seizures, glucose level was 37 mg/dl (NV>40), Na and K were normal. He had not history of parental consanguinity. He was born at term after an uneventful pregnancy and normal delivery. Birth weight, length and external genitalia were normal. To rule out inborn errors of metabolism brain MRI was performed at 6 days of life showing hyperintensity in T1 in basal ganglia and periaqueductal encephalic trunk. In the following days he presented poor weight gain and hypotony. Laboratory: Na 119 mEq/l (136-150), K 6.9 mEq/l (3.6-5.0). Cortisol 5.8ug/dl, adenocorticotropin (ACTH)>2000 pg/ml (< 46) Plasma 17-hydroxyprogesterone 1,2 ng/ml (< 4). Ammonia, lactic acid, amino acid, organic acid, acyl carnitine and renal function were normal. Direct sequencing of the coding exons and exon/intron-boundaries of the DAX-1 (NR0B1)-gene locus revealed the presence of c.1274G>C (p.R425T), in exon 2 which is a known mutation causing X-linked congenital adrenal hypoplasia, allowing diagnosis of the disease. Supplementation with hydrocortisone, fludrocortisone and salt normalized clinical situation. Magnetic resonance spectroscopy and neurological evaluation were normal at 2-yrs-old.
Conclusions: Transient brain MRI imaging can be found in AHC in the presence of hypoglycemia, without apparent involvement of electrolytes imbalance, which were detected later. Future studies will determinate prognosis in hypoglycemia associated to a transient brain imaging abnormalities.

P3-d1-1398 Perinatal and Neonatal Endocrinology 3

Reversible pulmonary hypertension caused by diazoxide therapy in patients with congenital hyperinsulinism

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Introduction: Congenital hyperinsulinism (HI) is a rare disorder causing severe hypoglycemia and brain damage. The mainstay of drug therapy is Diazoxide (Dz). Dz is considered a safe drug, however there are case reports of pulmonary hypertension (PH) occurring in patients on Dz. We report two patients with PH that was reversible upon discontinuation of Dz.
Case studies: A 3 day (d) old AGA male infant had recurrent episodes of apnea, seizure and hypoglycemia. HI was diagnosed on d 6. Prior to starting Dz he had an echocardiogram. which was normal and started Dz 15mg/kg/d. On d 5 of therapy he had a second normal echo. On d 13 he developed respiratory distress. The echo showed evidence of severe elevation of systolic RV pressure (70 mmHg), moderate RV dysfunction, bowing of the ventricular septum into the left ventricle supportive of severe elevation of the right ventricular pressure, and moderate to severe RV size with hypertrophy. He was ventilated with nitrous oxide and given oral sildenafil. 14 days after the d/c of Dz the PH was resolved and he fasted 9 hours without hypoglycemia.
A FT female weighing 2.6 kg had hypoglycemia on her first day of life. She required a GIR of 17 mg/kg/m and was diagnosed with HI and treated with Dz . Pre treatment with Dz her Echo revealed a small septal defect but was otherwise normal. She responded to Dz and was discharged home able to fast 9 hours. 6 w later she presented to the ER with a non hypoglycemic seizure. CXR showed cardiomegaly and echo showed showed a thickened right ventricle wall with adequate contractility, moderately dilated RV, and an estimated RV pressure of 80 mm Hg. Based on these findings a diagnosis of PH was made, Within a week of d/c Dz the PH had resolved. An echo one year later was normal.
Conclusions: These two patients illustrate that PH may be caused by Dz and that it is reversible if identified early. We suggest patients on Dz have a baseline echo and be observed for signs of PH.

P3-d1-1399 Perinatal and Neonatal Endocrinology 3

Anogenital distances in female and male Nigerian newborns, a descriptive study

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Background: A sensitive marker used by reproductive toxicologists in rodent experiments is anogenital distance (AGD). Numerous studies attest to its validity as a sensitive marker for the effects of in utero exposure to androgens and chemicals with anti androgen effects. In animal studies evaluating the effects of hormonally active agents, measurement of anogenital distance (AGD) is now routine and serves as a bioassay of fetal androgen action. There are very few human studies on anogenital distance and out of the few only one is an African Study.
Objective and hypotheses: To determine AGD in male and female Southwestern Nigerian newborns and relate this to other anthropometric measures.
Methods: A cross-sectional study was conducted among the newborn children of women admitted for delivery to the Adeoyo Maternity Hospital, Ibadan, Southwestern, Nigeria in 2009. A total number of 108 healthy male and 102 healthy female newborn babies delivered at gestational ages 28 weeks or more were enrolled in the study. Anthropometric measurements were taken of weight, length, head circumference, penile / clitoral sizes and AGD.
Results: The AGD measured was about two-fold greater in males (mean ± SD = 2.92 ± 0.43 mm) than in females (mean ± SD = 1.24 ± 0.29 mm).There was statistically significant relationship between the anogenital distance and the weights of both the females and males studied.
Conclusions: There is sexual dimorphism of AGD in humans as evident in the outcome of this study. More research is needed to evaluate the effect of hormonally active agent on AGD in Nigerian newborns.

P3-d1-1400 Perinatal and Neonatal Endocrinology 3

The prevalence of congenital hypothyroidism in the Republic of Bashkortostan, Russia: 20 years of neonatal screening

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Background: Congenital hypothyroidism is one of the most severe diseases of thyroid. Its prevalence reaches one case per 3500-4000 newborns. Screening examination of newborns allows making out diagnosis and starting treatment of hypothyroidism for the first weeks of life.
Objective and hypotheses: To determine the prevalence of congenital hypothyroidism in the Republic of Bashkortostan, Russia.
Methods: Level of thyroid stimulating hormone (TSH) in the whole blood of newborns was determined by immunofluorescence method with use of reagents "DELFIA Neonatal hTSH" on a "Victor" analyzer of the "WALLAK" Company. As the highest acceptable level (cut-off point), the TSH level higher than 20 μU/ml was taken. In the case of the elevated TSH level, determination of its concentration was repeated.
Results: Examined were 892807 newborns from 1993 to 2012. The examination of newborns by screening was 98.5%. The TSH level in the whole blood higher than 20 μU/ml was revealed in 8476 newborns (0.95%). In these children, levels of TSH, triiodothyronine, and free thyroxin in the blood serum were determined. Congenital hypothyroidism was diagnosed in 185 newborns. Among these patients, in 9 children (4.9%) the TSH concentration was in the range from 20 to 50 μU/ml, in 27 patients (14.6%) - from 50 to 100 μU/ml, in 149 (80.5%) - higher than 100 μU/ml. The median of the age, at which congenital hypothyroidism was diagnosed, amounted to 16 days (from 8 to 24 days).
Conclusions: The prevalence of congenital hypothyroidism in the Republic of Bashkortostan amounts to one case per 4825 newborns.

P3-d1-1401 Perinatal and Neonatal Endocrinology 3

An interesting presentation of septo-optic dyplasia and panhypopituitarism with collapse and liver failure

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Introduction: This case demonstrates the link between hypopituitarism and liver failure in neonates.
Case study: A five week old baby presented to the emergency department in a state of collapse with hypothermia, bradycardia and jaundice. The blood glucose at presentation was 0mmol/L. The baby was resuscitated with fluids and dextrose but continued to have high sugar requirements. He was in a state of liver failure with deranged clotting. A hypoglycaemia screen revealed cortisol levels
< 27nmol/L. An MRI subsequently demonstrated septo-optic dysplasia and endocrine investigations showed panhypopituitarism. The liver failure began to resolve with cortisol replacement.
Conclusion: Hypopituitarism is an unusual but reversible cause of cholestasis in neonates. A cortisol level should always be part of the investigation of cholestasis and liver failure in this age group.

P3-d1-1402 Perinatal and Neonatal Endocrinology 3

Relation of estimated birth brain weight to circulating insulin-like growth factor binding protein-3 in not-life-threatened newborns: an explanatory role for the part of birth body weight not attributable to estimated birth brain weight is recognizable independently of the presence of caesarean section

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Background: The involvement of fetal head in delivery mechanics is altered by Caesarean Section (CS).
Objective and hypotheses: We evaluated the role of that part of birth body weight (BW) not attributable to brain (NBBW) in relations of estimated birth brain weight (BRW) to human newborn (NWB) blood serum Insulin-like Growth Factor Binding Protein 3 (IB3), apart from possible influences of CS, birth gestational age in completed weeks (GA) ≤36 (preterm birth, PTB) and a BW< 10.th centile for GA (SGA).
Methods: 78 NWBs
1) with complete data for SEX, GA, BW, birth head circumference (HC), IB3 measured by RIA in uM/dL at one of the first 5 postnatal (PN) days (x), 5 days after x (y) and 10 days after x (z), and PN age at x in days (PNA) and
2) without any among life-threatening disease, diabetes mellitus (DM) and mother with DM were included in the study (males, n=43; CS, n=52; PTB, n=46, SGA, n=20; GA range=28-42; BW range=1200-4150gr).
Natural log-transformed IB3 (IB3-LN) resulted near-normally distributed. BRW was calculated through the formula "BRW= 0.037 x $HC^{2.57}$" according to McLennan-Lindley (units; BW and BRW=gr; HC=cm). NBBW was calculated as BW minus BRW. Multiple linear regression (MLR) was used (computations; male SEX, PTB, SGA and CS; condition present=1, otherwise=0).
Results: Tab.1 shows MLR models with IB3-LNx-y-z as outcome and as predictors either
1) BRW,SEX, PTB,CS,SGA and PNA (Tab.1A) or
2) BRW,SEX,PTB,CS,NBBW and PNA (Tab.1B) as BRW partial correlation coefficient (r)-t-p and MLR model R2-F-p.

A)	vs.	IB3-LNx	IB3-LNy	IB3-LNz	B)	vs.	IB3-LNx	IB3-LNy	IB3-LNz
BRW	r	.299a	.264a	.276a	BRW	r	-.033ns	-.055ns	-.169ns
	t	2.639	2.304	2.416		t	-0.282	-0.460	-1.445
	R2/F	.423/ 8.692b	.367/ 9.587b	.380/ 7.257b		R2/F	.523/ 12.954b	.533/ 13.493b	.567/ 15.467b
	Signif.:	a, p<.025;	b, p<.001;	ns, p not significant.					

[Tab.1.]

Conclusions: NBBW could be involved in BRW relations to IB3 not explained by CS, SEX, PTB, SGA and PNA as such in not-life-threatened NWBs.

P3-d1-1403 Perinatal and Neonatal Endocrinology 3

SGA and obesity: the importance of detecting metabolic risk backgrounds

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Background: In the past 20 years the prevalence of childhood obesity in Europe has increased dramatically. This trend has prompted the WHO has defined obesity as the "biggest non-infectious pandemic of the century".
Objective and hypotheses: The prevention and treatment of this problem may reduce the risk of complications in adulthood.
Method: Children obesity or weight-altering processes. We estimated gestational age and anthropometric variables to child birth, ethnicity, breastfeeding, age, sex, weight, height, BMI, fat mass and fat free.
Results: 160 patients: 54.4% (n = 87) 45.6% girls (n = 73) First consultation: 10.1 ± 2.2 (6-17). Mean maternal age at birth: 29.9 years (29.9 ± 5.2; 17-44) -. BMI> 97: 69.4%. This group had a higher percentage of body fat significantly. Breastfeeding: 85.7% No significant differences in the percentage of fat mass between being breastfed and those who did not. Distribution by ethnicity: 74.8% Caucasian. Maternal obesity: 35%. Weight and height at birth: 2.7% SGA, No statistical differences were found between maternal obesity and between weight and length at birth.
Conclusions: First contact with the consultation of 10 years, with a slightly higher percentage of girls Most received breast,% similar to the general population and it does not seem to influence the percentage of fat. A higher than expected rate in the general population are obese mother, but according to our data, obesity does not appear to influence the birth weight and length or percentage of fat. A percentage of Latins thanexpected prevalence is controlled by the consultation of obesity. Although this study may present a selection bias and a reminder, being retrospective, opens the door to future studies in our Center for evaluation of the different variables studied, especially in risk children, such as SGA in relation to the development of obesity in the infant period.

P3-d1-1404 Pituitary and Neuroendocrinology 5

Fanconi anemia presents as short stature in Yemenite siblings

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Background: Pancytopenia (PC) can be observed in growth hormone deficiency and typically resolves with recombinant growth hormone (rGH). Fanconi anemia (FA), a chromosomal breakage disorder, presents with bone marrow failure and malignancies early in life; it is associated with several endocrinopathies, including short stature.
Objective and hypotheses: To report:
(1) a sibling pair with short stature ultimately diagnosed with FA, and
(2) an association of FA with Celiac disease (CD).
Methods: Case report
Results: An 8 year-old Yemenite girl, born to first cousins, presented with short stature (ht -5.84 SD, wt -5.54 SD). CBC: WBC 3.3 $x10^9$/L, Hb 10.5g/dl, and platelets 102 x 10^9/L. Serum IGF-1 and IGFBP3 were low (25ng/ml; 1mcg/ml). Karyotype was normal. Screening antibody tests for CD were positive. MRI: pituitary stalk transection. With rGH, her growth velocity improved modestly (6.5cm/yr), but increased once a gluten-free diet was strictly implemented (10.5 cm/yr). Despite rGH, PC persisted and a bone marrow biopsy showed nonspecific hypocellularity. One year later, her younger full brother, then 8 years old, came from Yemen. His failure to thrive was severe (ht -7.75 SD, wt -14.2 SD). Notably, he had a left duplicate thumb. CBC: WBC 3.9 x10 ^{9}/L, Hb 11g/dl, and platelets 72 $x10^9$/L. IGF-1 was undetectable and IGF-BP3 was 0.6mcg/ml. MRI: underdeveloped pituitary gland. Diepoxybutane testing in both siblings supported diagnoses of FA.
Conclusions: Despite PC refractory to rGH, FA was overlooked until a sibling appeared with a specific FA feature. This report highlights the need to consider FA in patients with short stature and PC, particularly since in a premalignant condition rGH must be approached with added caution. The association of FA with CD has not yet been reported. It is worthwhile to screen a FA cohort for CD, especially in those with suboptimal rGH response, and particularly because CD can compound the risk for intestinal malignancies.

P3-d1-1405 Pituitary and Neuroendocrinology 5

Late diagnosis of congenital panhypopituitarism

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Introduction: Congenital Panhypopituitarism (CP) is usually diagnosed during first years of life, therefore few cases of natural course throughout adolescence or young adulthood have been reported.
Objective: To describe 4 cases of CP with late diagnoses because of oligosymptomatic presentation even though they presented 3 or more hormone deficits.
Material and methods: Charts of patients seen between January 2004 and December 2012 were revised. Patients who were diagnosed with CP at an age older than 14 years old were evaluated. CP was diagnosed when 2 or more pituitary hormones were affected.
Results: 4 patients met CP diagnosis criteria (1F/1M). All of them were referred because of short stature and 3 because of delayed puberty, without previous evaluation. Workup showed TSH, ACTH and GH deficits in 4 patients and FSH and LH in 3. Images revealed pituitary hypoplasia with stalk absence in 4 patients and ectopic posterior pituitary in 3 of them. None of them had diabetes insipidus. Height SDs were between - 4,6 and - 6,8. All of them had learning difficulties and couldn't complete formal education.
Discussion: Presentation of CP may vary from severe neonatal hypoglycemia and cholestasis to late presentation because of short stature or delayed puberty at adolescence or infertility or sexual dysfunction in adulthood. Our 4 patients delayed medical attention because they were oligosymptomatic or because of socioeconomic reasons.
Conclusion: There are still patients with CP who are not evaluated until adolescence or adulthood, and this may compromised their quality of life, because of adult short stature, late onset of puberty, less academic achivements and the deleterious effect in body composition.

P3-d1-1406 Pituitary and Neuroendocrinology 5

Rapid onset obesity, endocrine hypertension and ganglioneuroblastoma intermixed: early manifestation of ROHHAD-NET syndrome?

Presentation of two cases

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Background: ROHHAD-NET is a rare condition characterized by central hypoventilation,rapid onset obesity, hypothalamic involvement and neural crest tumours, unpredictably arising during childhood. Since obesity is one of the first symptoms associated with some endocrinopathies, pediatric endocrinologist may be early involved in management of these cases and should suspect this syndrome, along with other causes of genetic obesity.
Objective and hypotheses: The aim is to describe two cases with early severe obesity and suspicious early stage of ROHHAD-NET syndrome.
Case study: Two patients(pts) were referred to our centre in the last 2 years for severe obesity, hyperreninemic hypertension and in one case suspicious Cushing syndrome. The clinical data are reported in table. In both cases an abdominal mass was detected by ultrasonography performed to exclude renal hypertension and Cushing syndrome. Histology result was in both cases ganglioneuroblastoma intermixed (GN). Case 2 showed only morning hypercortisolism, immunostaining of GN was negative for ACTH cells. After tumor removal in case 1 obesity improved while hypertension persisted; in case 2, BMI worsened while hypertension resolved. In both cases, polysomnography did not show hypoventilation. Both patients showed regular growth along familiar target height, however severe GH deficiency was found in case 2 with mild hyperprolactinemia.
Conclusions: Although respiratory involvement is absent in our cases, in our opinion ROHHAD-NET should be suspected considering the constellation of pathological features as endocrine disturbances, early and rapid onset obesity, neural crest tumour. Since the lack of specific diagnostic tests, known genetic background and the chance of an evolutive phenotype we planned careful monitoring of these patients, to early detect any worsening of respiratory function.

P3-d1-1407 Pituitary and Neuroendocrinology 5

Severe hypothalamo-pituitary dysfunction accompanied by influenza-associated encephalopathy

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Background: Acute encephalopathy often leads to severe neurological damage and may cause acquired hypothalamopituitary dysfunction, which can result in severe morbidity and even death. We herein describe two pediatric patients with hypopituitarism accompanied by severe influenza-associated encephalopathy.
Objective: They were 1-year-old male and 5-year-old girl patients. They diagnosed with acute necrotizing encephalopathy and postresuscitation encephalopathy. Both showed unstable vital signs and evidence of multiple pituitary hormone deficiency by the hormonal analysis.
Methods: We performed hormone replacement therapy of adrenal, thyroid and antidiuretic hormones.
Results: They continued cardiac activity and resulted in prolonged survival.
Conclusions: Screening for endocrine dysfunction is important in patients with hypothalamopituitary dysfunction associated with severe central nervous system dysfunction. There are few reports of hypopituitarism in pediatric patients with central nervous system damage. We must accumulate these cases and arrive at a consensus for therapy, including hormone replacement.

	Case 1 (1y2m, male)	Case 2 (5y, female)
Intensive therapy	Mechanical ventiration, Brain hypothermia, Steroid pulse	Mechanical ventiration, Brain hypothermia, Steroid pulse
Adrenal function	ACTH <2.0pg/ml, Cortisol 3.0μg/dl	ACTH <2.0pg/ml, Cortisol 1.3μg/dl
Thyroid function	TSH 0.13μIU/ml, fT4 0.62ng/ml	TSH 3.73μIU/ml, fT4 0.17ng/ml
Antidiuretic hormon	ADH 1.1pg/ml	ADH 1.0pg/ml

[Summery of clinical and endocrine characteristics.]

P3-d1-1408 Pituitary and Neuroendocrinology 5

Endocrine management of sellar lesions in children

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Background: In sellar masses a precise diagnosis is of importance since specific therapy will depend on it. Not all of them require surgery.
Objective and hypotheses: To emphasize that endocrine testing should be mandatory for sellar masses, identifying those in which hormonal treatment is first line of therapy, and to describe presenting symptoms and endocrine abnormalities on follow-up.
Methods: We reviewed the records of children aged under fourteen who were treated in our institution over twelve years. Data were collected concerning sex, age, lesion nature, clinical presentation, size, treatment, and endocrine abnormalities.
Results: We studied 43 patients (25 female), aged 7.2 ±4.1 years (range 0.25-13.5). The follow-up period was 6.2 ± 3.7 years. We knew lesion nature in 38 cases and endocrine management was first line of treatment for four: three prolactinomas (dopamine agonist) and one thyrotroph cell hyperplasia (levothyroxine). The most common presenting symptoms were neurologic and/or visual (24/43), followed by endocrine complaints (13/43). The endocrine symptom interval was 12.6 ± 18.2 months and the neuro-ophthalmic one 2.6 ± 4.9 ($p = 0.012$). At initial evaluation 26/43 patients presented any endocrine abnormality, raising to 36/43 at the end of follow-up period.
Conclusions: The management of sellar lesions involves a multidisciplinary effort. Detailed endocrinologic testing should be mandatory for these patients. Hormonal management was first line of treatment for some of them. Endocrine disorders usually occurred before neurological and ophthalmological symptoms, so identifying them may help to earlier diagnosis. Hormonal evaluation is mandatory as well on follow-up.

P3-d1-1409 Pituitary and Neuroendocrinology 5

Clinical characteristics and evolving syndrome of pituitary stalk interruption

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Background: Syndrome of pituitary stalk interruption (SITP) is an abnormal hypothalamic pituitary region on MRI. It combines pituitary hypoplasia ± interruption of the pituitary stalk ± post ectopic pituitary.It is associated with congenital malformations of the midline and hypopituitarism.
Objective and hypotheses: Report the clinical, paraclinical and evolving of this Syndrome.
Methods: 67 patients (57 ♂ , 10 ♀) carrying a SITP were followed. These children were consulted for delay stature n = 65 and polyropolydipsic syndrome n: 2. They received a complete physical examination, hormonal exploration (insulin and glucagon / propranolol / GH, IGF1, FT4, TSH, insulin / blood cortisol, ACTH, prolactin), and urine specific gravity ± Test fluid restriction. The gonadotropic axis was not evaluated due to non-pubertal bone age. Patients were regularly evaluated.
Results: There was a male predominance (sex ratio: 1.7). The average age at diagnosis was 8 ± 3.4 years (03-18). obstructed labor was noted in 10 cases (breech presentation: n: 6 and forceps n: 2). Neonatal hypoxia was reported in two cases. The average size was - 4.8 ± DS / M Sempé and Pedron (- 2 - 7). Micropenis ± cryptorchidism were present in half of the boys.
Facio abdominal malformations were found in 53 cases. Hormonal evaluation revealed a growth hormone deficiency in all cases. This deficit was associated with other anterior pituitary deficiencies in 44 cases. Diabetes insipidus was found in 02 cases.
MRI showed the presence of other intracranial malformations in half the cases.
Conclusions: The SITP is a cause of growth hormone deficiency important to recognize. Its diagnosis when exploring a causal failure to thrive. The GHD is usually constant. It can be associated with other pituitary deficits. His discovery leads to recherch congenital malformations associated and regular reassessments.

P3-d1-1410 Pituitary and Neuroendocrinology 5

Female paediatric and adolescent prolactinomas

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Introduction: Our aim is to study the frequency, clinical, biological, and radiological characteristics of female prolactinomas and their complications in childhood and adolescence.
Subjects and methods: The studied population is composed of 32 girls (≤16years), adolescents (≤ 20) and women suffering from primary amenorrhea due to prolactinomas. In this retrospective study (1980-2012), prolactinoma's diagnosis was based on clinical, biological, radiological ± pathological and immuno-histochemical studies. All had hormonal assessment including prolactin, estradiol, FSH, LH, cortisol, GH±IGF1, TSH, FT4, and ophthalmological examination. Cerebral exploration was based on CT scan and MRI.
Results: Among 153 female prolactinomas 32 were paediatric forms (20.9%), mean age=18.78 ± 9years (12- 30). 5= 15.62% were under 16. The majority (93.54%) consulted for menstrual troubles, 50% had primary amenorrhea. An Overweight was observed in 23.35%, galactorrhea in 78.12% and ophthalmological abnormalities in 43.75%. Mean prolactin= 512.97ng/ml (106-6000). Mean height=12.71mm (4- 50mm). Only 2 were giant (≥4cm) and 2 look like craniopharyngiomas. The tumour was invasive in 22.58% and reached the chiasmatic area in 32.25%. Gonadal deficit was observed in all. 2 or more pituitary deficits were seen in 15.62%, and diabetes insipidus in one case. Neurological complications were absents.
Conclusion: In our population**,** paediatric female prolactinomas account for 1/5 of female cases. Only 15.62% were diagnosed before 16. Macro lesions are as frequent as micro and iso-adenomas, but giant and invasive tumours are rare which explains the rarity of neurological complications.

P3-d1-1411 Pituitary and Neuroendocrinology 5

Endocrine disorders after craniopharyngioma treatment in children: a retrospective study

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Background: Craniopharyngiomas correspond to 1.2-4% of intracranial tumors in childhood. Despite being benign, they have high morbidity due to their location. Endocrine disorders may be present at diagnosis or as a result of treatment.
Objective: To retrospectively investigate endocrine disorders in children after craniopharyngioma treatment.
Population/methods: Nineteen patients (11 girls) aged 5.7±3.8 years, referred between 1996-2011, had their medical histories reviewed in the first 3 years after treatment (surgery, radiotherapy, chemotherapy). Anthropometric data (weight, height, BMI), hormone deficiencies (IGF-1/IGFBP-3, TSH/T4L, ACTH/cortisol, LH/FSH, diabetes insipidus) and dyslipidemia (total cholesterol≥200mg/dL, LDL≥130 mg/dL, triglycerides≥130mg/dL) were investigated.
Results: In the first, second and third year of follow-up, the percentages of endocrine disorders found were, respectively: diabetes insipidus: 89%, 89% and 89%; hypocortisolism: 89%, 89% and 89%; central hypotiroidism: 68%, 89% and 89%; growth hormone deficiency: 47%, 79% and 89%; gonadotropin deficiency: 5%, 5% and 6%; decreased growth velocity: 42%, 42% and 44%; obesity or overweigth: 58%, 63% and 61%. 13 out of 14 patients (93%) whose lipid profile was evaluated presented dyslipidemia.
Conclusion: Endocrine disturbances were found at the beginning of follow-up and continued to appear during the study period, indicating the importance of early referral to the pediatric endocrinologist.

P3-d2-1412 Pituitary and Neuroendocrinology 5

Paediatric male prolactinomas: response to medical treatment

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Introduction: Our goal is to study the response of paediatric and adolescents male prolactinomas to medical treatment based on dopamine agonists.
Subjects and methods: 14 boys and adolescents with prolactinomas [mean tumour height= 25.32mm (15-65.5mm), mean prolactin=3569.51ng/ml (124-22728)] were analyzed before and after medical treatment (bromocriptine=13, cabergoline=1), mean dose bromocriptine= 24.48 mg/j (5-50mg), and mean duration= 32months (1- 196).
Results: The tolerance was good in 12 cases = 85.71%. Stature and pubertal development were achieved in respectively 100% and 57.14%, Galactorrhea disappeared in 75%, but gynecomastia persisted. Prolactin was normalized in only 28.71% and testosterone in 62.5%. Tumour reduction ≥30% was observed in 85.71% and vision improvement was found in 42.85%.
Conclusion: Paediatric and adolescent male prolactinomas are sensitive to medical treatment as tumour reduction was observed in 85%, but prolactin inhibition was mediocre probably because of poor daily compliance and fear of high dose bromocriptine.

P3-d2-1413 Pituitary and Neuroendocrinology 6

Diabetes insipidus (DI) in a premature infant with severe intraventricular hemorrhage (IVH)

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Introduction: IVH is common in premature and very low birth weight infants with an incidence of approximately 20%. However central DI is a rare complication of IVH.
Case study: A 30 weeks gestation male underwent traumatic birth with subsequent grade 4 IVH. Serial ultrasounds showed increasing ventricular size bilaterally. Baby's medical history was also significant for respiratory distress (requiring intubation/ventilation), hyperbilirubinemia and anemia. He developed mild hypernatremia within the first 5 days of life, raising concern for DI, however was managed with supplemental intravenous fluid therapy. He required ventriculo-peritoneal shunt placement at 4 weeks of age. The following day, serum sodium increased from upper 140's (mmol/L) to mid 150's. Subsequently urine output (UOP) reached 7 ml/kg/hr, sodium levels increased to upper 150's,serum and urine osmolality were consistent with diabetes insipidus at 327 mOsm/kg and 107 mOsm/kg, respectively. Therapy was initiated with chlorothiazide (CTZ), however, UOP continued to increase to 17 ml/kg/hr. Therefore CTZ was discontinued and a vasopressin drip was started at 0.05mU/kg/hr. The drip required frequent titration and adjustment of fluids to maintain sodium within goal range of 140-150. He required dosing as high as 0.55 mU/kg/hr. Evaluation for function of other pituitary hormones revealed normal thyroid function tests and an abnormal high dose ACTH test (0 min: 13.8 mc/dL 60 min: 17.1 mcg/dL). Hydrocortisone treatment was initiated, but a repeat ACTH test will be performed if DI resolves in the future. Magnetic resonance imaging of the brain showed the faint presence of a posterior pituitary bright spot.
Conclusion: Both transient and permanent DI as a result of IVH can be seen in the neonatal period. Time will determine, if our case is transient. Treatment with vasopressin drip worked well to manage DI in a critically ill preterm baby without causing extreme fluctuations in sodium levels.

P3-d2-1414 Pituitary and Neuroendocrinology 6

Obesity in patients with childhood pituitary adenomas is unlikely to be related to treatment or hormone replacement therapies

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Background: We recently reported an increased prevalence of obesity, metabolic and cardiovascular risk factors in adult patients with pituitary adenomas diagnosed in childhood (1).
Objective and hypotheses: Obesity is an inherent characteristic of patients with pituitary adenomas, unrelated to treatment or pituitary function.
Methods: Retrospective data were collected from 16 patients with pituitary adenomas treated since 2000.
Results: 4 patients (3M) median age 10.3 yrs (range 4.2 - 15.3), had Cushings Disease (CD), 8 patients age 14.6yrs (13.4-16.1) had prolactinomas (Prl) and 4 patients age 15yrs (13.3-16.6) non functioning adenomas (NFA). BMI at diagnosis was: CD 3.5 (2.1-5.5), Prl 3.0 (-0.5 - 4.0), NFA 2.0 (1.2 - 4.5). All patients with CD and NFA were treated with transphenoidal surgery (TSS) and 1 patient with NFA also required radiotherapy, all patients with Prl were treated with bromocriptine / cabergoline, and 1 had TSS.After 2.5yrs (1.5 - 3.0) BMI SDS was 2.4 (0.4 - 3.7) in CD, after 2.3yrs (0.3 - 2.5) BMI SDS was 3.0 (-1.1 - 3.5) in Prl, and after 2.7 yrs (1.5-4.3) BMI SDS was 2.1 (-0.5 to 2.3) in NFA. Endocrine therapy at most recent review: CD: growth hormone (GH) (N=4) hydrocortisone (HC) (N=4), thyroxine (N=2), testosterone (N=1), NFA: HC (N=1) and GH (N=1), Prl: intact pituitary function.
Conclusions: Data from this small cohort of patients suggest that obesity is an intrinsic characteristic of patients with pituitary adenomas in childhood. BMI SDS at follow up was highest in those with Prl, all of whom had intact pituitary function, and only one of whom underwent surgery. These preliminary data suggest that obesity is unrelated to treatment or endocrine therapy. Weight management should start at diagnosis.

P3-d2-1415 Pituitary and Neuroendocrinology 6

Syndrome of inappropriate antidiuretic hormone secretion (SIADH): a challenge in diagnosis and therapy

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Introduction: The SIADH remains a challenge in terms of etiologic diagnosis and therapy. It occurs in various benign and malignant conditions, in particular morphological anomalies of the central nervous system (CNS), tumours, lung diseases and the use of drugs.
Case report: A 3 year old twin girl with a history of cleft lip and palate surgical repaired. She was asymptomatic when hyponatremia was detected in a routine analytical study. The SIADH was diagnosed: low serum sodium: 123 mEq/L, low serum osmolality: 256 mOsmol/L, inappropriately elevated urinary osmolality: 434 mOsmol/L, urinary sodium: 57mEq/L, normal serum creatinine and normal acid-base balance. To exclude hormonal deficits associated with midline defects, a endocrinological study was done and showed low serum level of IGF1: 25,4 ng/dl, IGFBP3, cortisol and thyroid function were normal. A glucagon stimulation test revealed normal growth hormone and cortisol. A 24hour urine test showed fractional excretion of Na+ 0.6%. Chest X-ray, brain MRI and FDG-PET scan were normal. Serum level of antidiuretic hormone slightly increased: 5.5 pg/ml. She was treated with fluid restriction (500ml/dia) and supplement of Na + (1mEq/kg/day) with slight improvement of hyponatremia: 129 mEq/L. By keeping hyponatremia, it was decided to start furosemide 0.5 mg/kg/day, showing improvement of hyponatremia: 133 mEq/L. Mainly due to the failure of water restriction, keeps some instability in the values of Na+.
Discussion: In cases of ill-defined abnormalities CNS associated with SIADH it's difficult to establish a cause-effect relationship, so it's important to exclude other causes. The therapy approach remains a challenge, because the adherence to fluid restriction is difficult. The use of furosemide in asymptomatic patients remains controversial.
However, there was a positive response in this case. To avoid any neurological sequelae, it's important to follow-up tight, with gradual correction of hyponatremia.

P3-d2-1416 Pituitary and Neuroendocrinology 6

Familial hypopituitarism with pituitary stalk interruption syndrome

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Aim: Pituitary stalk interruption syndrome (PSIS) is a rare morphologic anomaly responsible of hypopituitarism. Habitually it occurs as a sporadic disease but familial forms are rarely reported. The aim of our study is to analyze the clinical, biological and morphological aspect of PSIS in the same family.
Observations: The index case presented at 16 years for severe short stature and delayed puberty. Hormonal assessment argued for combined pituitary deficiency of growth hormone (GH), thyrotropin (TSH) and gonadotrpin (GnRH). MRI showed typical image of PSIS with stalk interruption, pituitary hypoplasia and ectopic posterior pituitary. Family history showed two older brothers 26 and 31 years old who were short. Their laboratory results showed isolated somatotropin deficiency. The MRI showed the same typical image of PSIS in the patient aged 26. In the other brother the MRI showed only the absence of posterior pituitary.
Conclusion: Familial pituitary stalk interruption syndrome remains rare with clinical, biological and radiological polymorphism. It is responsible of variable pituitary deficiency that may be progressive leading to panhypopituitarism. Hence it mandates a regular assessment of pituitary function.

P3-d2-1417 Pituitary and Neuroendocrinology 6

Pituitary stalk tuberculosis: difficult diagnosis

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Introduction: Schoolgirl with hipopituitarism due to stalk tuberculosis without compromising another organ.
Case study: We report a female patient 6 years old, who was referred for poor growth velocity, and below target height, bone age delayed; we diagnose central hypothyroidism, diabetes insipidus and growth hormonal deficiency. A magnetic resonance MR shows hypothalamic-hypophyseal thickened; we carry out PCR and concluding stalk tuberculosis (Mycobacterium tuberculosis) without pulmonary compromise. She was treated antituberculosis therapy with successful following.
Conclusions: Tuberculosis infections incidence has increased all around the world and stalk pituitary compromise in pediatrics is uncommon. We should consider tuberculosis in patients showing thickened stalk and hipopituitarism.

P3-d2-1418 Pituitary and Neuroendocrinology 6

Phenotypic and evolutionary diabetes insipidus of childhood

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Background: Diabetes insipidus (DI) is a rare disease of the child. Its symptoms is sudden and significant and its evolution depends on the etiology.
Objective and hypotheses:Enjoy characterizations clinical, etiological and evolutionary DI of children.
Methods: 30 children with DI were hospitalized in 15 years. Following an interview and a clinical examination, paraclinical exploration is performed:, balance nonspecific, erythrocyte sedimentation rate, measurement of CRP, electrolytes , blood and urine specific gravity. The exploration was completed by a water deprivation test, a report earlier pituitary MRI HH, radiographs skeleton and embryonic tumor markers. Patients are put under AVP and specifically addressed. Revaluations are performed.
Results: The average age of 8.5 years [01 - 15]. The SPP is sharp and significant in all cases. The delay between the onset of the SPP and the consultation is 01 year (6 months - 6 years). SPP resulted sleep disorders in children 3 and dehydration in two cases. The DI is central in 76.6% of cases with an etiology in 18 cases: ITP syndrome (n = 4), idiopathic infindibulite (n = 2), histiocytosis (n = 1), germinoma (n = 1), craniopharingiome: (n: 10). primary polydipsia is noted in both cases, the results showed hypopituitarism divorced in lesions organiques.Une regression of symptoms in AVP was noted in all cases. The disappearance of DI is observed after radiotherapy germinoma. Biological controls and neuroradiological other children were stationary six years after.
Conclusions: DI particularly difficult in young children can lead to complications, neurological disorders and sleep disterbances. Etiologies are dominated by the tumor lesions. If the cause is not identified, we should continue monitoring.

P3-d2-1419 Pituitary and Neuroendocrinology 6

Holoprosencephaly and pituitary deficiency

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Background: Holoprosencephaly is a brain malformation resulting from incomplete cleavage of the prosencephalon, occurring between the 18th and the 28th days of gestation, four subtypes are described, sometimes it may be familial. Facial anomalies, developmental delay and neurological disorders are the main manifestations but endocrine dysfunction is also frequently reported. We reported the observation of a male patient who presented at 18 years for growth retardation and pubertal delay, hormonal assessment showed growth hormone and gonadotrophins deficiencies, other pituitary functions were normal. MRI imaging found holoprosencéphaly and triventricular hydrocephaly but without radiological anomalies of pituitary or pituitary stalk. The patient was treated with growth hormone with a good growth catching and after that he was treated with androgens; hydrocephaly which was only monitored was stable over time.
Holoprosencephaly requires a multidisciplinary management; its prognosis depends on the severity of the disease and associated complications.

P3-d2-1420 Pituitary and Neuroendocrinology 6

Hypoglycaemia and hepatic failure in an infant with congenital hypopituitarism

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Background: Colestasis and coagulopathy are clasics symptoms of hepatic failure due to metabolic disease and bliar atresia, however the hepatic ducts are dependent of normal pituitary function after delivery, the assosiation of hypoglycemia and colestasis with coagulopathy may be confusional factor to anatomical or metabolical abnormalities in the first months of life.
Objective and hypotheses: Describe the clinical suspect of hypopituitarism in one child with hepatic transplant criteria, with recurrent hypoglycemia, colesthasis and micropenis.
Methods: We decide realize critical sample before metabolic anallysis of organic acydemias and biliar duct integrity due to micropenis in this seriouslly ill child.
Results: The Growth hormone and cortisol was severe inapropiated in hypoglycemia, MRI was made with ectopic neurophypophysis and empty sella. hypothyroxinemia was assosiated. with cortisol and growth hormone a low dose, the infant develoment transient hyperglycemia 5 days after cortisol start, we initiated lñevothyroxin, the anemia response was dramatic and progresive the coagulation factors and transaminases and bilirrubin was normalized. at 6 month the child was without colestasis treatmente and the rate of growt was normal, at year o f age, hepatic function are normal, and the facial apareance change with resolution of some dysmorphysm in the first months of life.
Conclusions: In any patient with hepatic dysfunction asosiated to hypoglycemia, hypopituitarism must be consider, most important in a masculine infant with micropenis.

P3-d2-1421 Pituitary and Neuroendocrinology 6

Neuropsychiatric symptoms in a patient with short stature with delayed diagnosis due to atypical presentation

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Background: Short sature and Failure to Thrive are very frequent patologies in pediatric clinics, however the spectrum of the patologies to consider is very large and sometimes confusing. The clinical not always it's easy to correlate with the evolution of the patient and the test interpretation requiere skills in the follow up
Objective and hypotheses: Describe one patient with Mutation in ADH receptor gene which was in follow up due to TUbular renal acydosis and stunjning growth, irritability and agitation episodes was follow up, ADH determination after emnergency psiquiatric symptoms in follow to seriously Hypernatremia with normal hydric restriction test make the way to found the diagnosis.
Methods: PCR Xq28, for nephrogenic insipidous diabetes; ADH elisa kit
Results: Inapropiate elevated ADH was found with serious ly matinal hypernatremia and hypostenuria, the patient was excelent response to los solute load diet amd hydrochlorotiazide, whit clinical confirmation we proceed to make molecular study for genetic counseling.
Conclusions: Strickly correlartion between serum and uirine somolar relation make the confirmation diagnostic, the psychiatric symptoms not was related to metabolic disease and the TRA was due to choronic dehydratation with

associated failure to thrive. The Growth curve is presented and the dificultd evolution of this child.
The counfounding factor was the restriction test negative for ID, but this was due to time without renal load previos to the test.

P3-d1-1422 Puberty and Gonads 9

Longitudinal evaluation of patients with autonomous ovarian follicular cysts

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Background: The development of autonomous functional ovarian follicular cysts results in pseudoprecocious puberty. However, the effects of the disease on long-term ovarian function and adult height in patients, who develop these cysts during childhood, are unclear.
Objective: The purpose of this study was to retrospectively investigate the clinical findings of autonomous ovarian follicular cysts. In addition, we discuss its effects on long-term ovarian function and adult height.
Patients: Ten female patients (age, 4.1-8.8 years; mean age, 6.4 years) were referred to our institution for vaginal bleeding. Of these, five patients had already reported breast development. However, the interval from breast development to genital bleeding was very short
(2 weeks-6 months). Two patients were diagnosed with McCune-Albright syndrome (MAS). Ovarian cysts were detected by ultrasound or magnetic resonance imaging in all the 10 patients, along with undetectable LH and FSH levels accompanied by high E2 levels.
Results: Each of the two girls with MAS developed recurrent vaginal bleeding three and five times, respectively. Of the other eight patients, vaginal bleeding occurred eight times in one patient, and the remaining seven patients suffered only one or two episodes. Currently, the patients are 8-22-years-old. Gonadotropin levels began to increase at the age of 8.8-11.3 years. Two of the girls (8- and 11-years-old) have not experienced menstruation yet. All the other girls have experienced regular menstruation cycles beginning at the age of 11-12 years. We have confirmed adult heights of 153.0-164.1 cm [mean 160.1 cm, +0.38 SD above the mean, although SD for the adjusted parental height was −0.28] in seven patients.
Conclusions: The vaginal bleeding episodes were not frequent in most of the patients except those with MAS, and long-term ovarian function might probably be normal. Although symptoms occurred at a younger age, their adult height might be within normal limits.

P3-d1-1423 Puberty and Gonads 9

Evaluation of adolescent girls with hyperandrogenism

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Background: Hyperandrogenism(HA) is mostly presented as polycystic ovary syndrome (PCOS). Non-classical congenital adrenal hyperplasia (NCCAH) is the main differential diagnosis to PCOS. The insulin resistance (IR) and obesity are commonly reliated with HA and must be considered for the most approporiate therapy.
Objectives: The aim of our study was to evaluate the etiology of HA in our patients, concomittance of IR, obesity and to reveal our therapy method.
Methods: 72 adolescent girls with HA were involved in this study. Oral glucose tolerance test(OGTT), ACTH stimulation and serum lipid profile tests were performed in all patients. HOMA-IR level higher than 3,5 was considered as IR. Peak 17-OH progesteron level after ACTH stimulation higher than 12 ng/dl was considered as NCCAH. Pelvic ultrasound was performed in all. 17-OH progesteron response to LHRH stimulation was evaluated in 32 patients, levels higher than 2ng/dl was considered as functional ovarian hyperandrogenism (FOH).
Results: The mean age was 15,21±1,39 years. Hirsutism (66,7%n=48) and menstrual irregularity (62,5%, n=45) were the complaints. 40% (n=29) of the patients had both. At the physical examination, %49 (n=35) of the patients were obese and %27,8 (n=20) were over-weight. Based on ACTH testing, 6(%8) patients were considered as NCCAH. Among the patients that LHRH test was performed 14(44%) had FOH. Insulin resistance was determined at 75% of all. There was no significant difference in HOMA-IR of patients with or without hirsutism and menstrual irregularity. Six patients had Hashimoto thyroiditis, one patient had impaired glucose tolerance. Metformin, oral contraceptives, spironolactone, and hydrocortisone treatments were applied to patients with IR, FOH, idiopathic HA, and NCCAH respectively.
Conclusions: The etiology of HA should be determined in order to choose the most beneficial treatment method for the patient. İn this respect, long termed follow up of our patients would be more informative.

P3-d1-1424 Puberty and Gonads 9

Extreme minipuberty presenting with vaginal bleeding in a 5-month-old preterm girl

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Introduction: Transient activation of Hypothalamic pituitary gonadal (HPG) axis can cause a mini-puberty (MP) in the neonatal period. It is often asymptomatic or results in transient thelarche. However, premature female infants can demonstrate enhanced activation of the HPG axis during MP. Precocious puberty in girls younger than age 2 years is unusual and mostly of peripheral in origin.
Case study: A 5-month-old , former 25 week gestation, premature female infant developed vaginal bleeding (VB). Medical history inculded a resolving grade 2 intraventricular Hemorrhage (IVH) , bronchopulmonary dysplasia, retinopathy of prematurity, GERD, trachebronchomalacia, apnea and anemia. Physical examination showed estrogenized vaginal mucosa, blood at the vaginal introitus and tanner 2 breast buds. Initial work up included: LH,FSH, estradiol, pelvic ultrasound (PUS), and MRI of brain. Results showed, LH: 3.6 mIU/mL (prepubertal < 0.3), FSH: 5.5 mIU/mL (prepubertal 0.5-3.7), and estradiol: 47 pg/mL. PUS showed mild endometrial thickening and ovaries with follicles measuring 0.81 mL and 2.53 mL. MRI showed no abnormalities of the pituitary or hypothalamus, and a resolving IVH. VB continued for 5 days. Leuprolide stimulation testing performed a day after the end of VB showed at 120 minutes a LH: 20.1 mIU/mL, FSH: 23 mIU/mL, and estradiol: < 5 pg/mL, which is a pubertal response. Two weeks later a second episode of scant VB occurred. Repeat LH and FSH were 6.7 mIU/mL and 8 mIU/mL, respectively. Option of Gonadotropin Releasing hormone (GnRH)agonist therapy was discussed with parents and a decision was made to start treatment if VB recurs or if there is an advancement in puberty.
Conclusion: VB can be a rare manifestation of minipuberty. Premature females may demonstrate extreme MP with greater elevation of LH in comparison to their full term counterparts. Given the transient nature, this may require no treatment, or only short term treatment with a GnRH agonists.

P3-d1-1425 Puberty and Gonads 9

An unusual case of primary amenorrhea and short stature: ovarian resistance syndrome

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Background: Ovarian resistance syndrome is unusual cause of primary amenorrhea, sexual infantilism and hypergonadotropic hypogonadism (HHG).
Case: A 15.5-year-old girl presented with lack of pubertal development, primary amenorrhea, and parental concern about severe growth retardation. She was the second child of first degree consanguineous parents. On physical examination, she was pre-pubertal with Tanner stage I breast development and no pubic or axillary hair. She had no clinical stigmata of Turner syndrome and her karyotype was 46,XX. Her height of 146.7 cm (-2.48 SDS) was below the first percentile.
However she had no clinical stigmata of Turner syndrome, clinical presentation of the case led to believe that the etiologies of primary amenorrhea, sexual infantilism and short stature were Turner syndrome, gonadal dysgenesis or premature (autoimmune) ovarian failure.
Results: A baseline blood screen (urea, electrolytes, liver enzymes, and full blood count) and thyroid function were all normal. Serum gonadotropins and sex steroid (FSH, 98 mIU/ml and LH, 42 mIU/ml, estradiol 9.2 pg/ml, pro-

gesterone 0.6 ng/ml) measurements revealed the diagnosis of HHG. Steroid-cell antibodies (St-C-Abs) was negative.
Pelvic ultrasound revealed small uterus (39 mm and 9 mm diameters) and small right ovary (15 mm and 11 mm diameters). Diagnostic laparoscopy showed two ovaries and small uterus. Ovarian biopsy proved abundant primordial follicles and spindle cell stroma without evidence of antral follicles (Fig 1), which point to the diagnosis of gonadotropins resistant ovary syndrome.
Conclusion: However, resistant ovary syndrome related with gonadotropins receptor mutation is extremely rare cause of HHG in pediatric endocrinology clinics, it should be in differential diagnosis of HHG in 46,XX patients with delayed puberty, primary amenorrhea and short stature.

P3-d1-1426 Puberty and Gonads 9

Van Wyk Grumbach syndrome: case report

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Introduction: Van Wyk Grumbach syndrom was discribed in 1960, and associates severe prolonged hypothyroidism, delayed bone age reduction in growth rate and incomplete isosexual precocious puberty GnRH independant with multicystic enlarged ovaries reversal following thyroid hormone replacement therapy,
Case study: We report the case of a 10 year old daughter, who has a primary hypothyroidism with poor academic performance, labeled autoimmune by the high rate of thyroid peroxidase antibody, Imaging CT to evaluate her walking disorders revealed a pituitary macroadenoma (13.5cm), and she has been having regular menstrual cycles, pubertal Tanner stage was breast 1 and pubic hair 2, with normal stature and no goiter. with levothyroxine treatment there has been a regression of macroadenoma and vaginal bleeding but persistent delay school, a karyotype was done objectifying mosaic trisomy 21.
Conclusions: The mecanism of precosious puberty in VWGS is uncertain, van wyk and grumbach explained it by a lack of specificity in the feedback mecanism therefore an overproduction of same hormones, the high circulating levels of TSH may intervene in FSH receptor, the most common cause of hypothyroidism in this cases is autoimmune thyroiditis and enlarged pituitary may correspond to thyrotroph hyperplasia.

P3-d1-1427 Puberty and Gonads 9

Mature teratoma in paediatrics: a case report

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Background: Ovarian tumors are uncommon lesions in children and adolescents. The actual incidence of ovarían lesions in Young girls is unknown. An approximate incidence has been estimated as 2,6 cases annually /100.000 girls and malignant ovarian tumors comprise about 1% of all childhood cancers.
The most frequent hystologyc type is the Teratoma. Although most are benign >80%, some contain immature or malignant elements, with the incidence or malignancy varying by location and age. Mature teratomas, also termed dermoid cysts, frequently contain hair, teeth, and sebum, especially in the ovaries. Ovarian tumors may present with acute abdominal pain, a large pelvic or abdominal mass or concerns of malignancy.
Objectives: To describe a pediatric patient with an immature of the ovary.
Material and methods: A seven years old girl with a five months history of pubarche, without thelarche or acne, diffuse abdominal pain but no abdominal masses palpable. Abdominal ultrasonography sowed an ovarian cyst. CT revealed a 5.0x4.4 cm hypodensa ovarian mass. Serum testosterone < 10 ng/dl, DHEA-S 66,.2 mcg/dl,17ohp 41ng/dl LH and FSH normal, bone age 8 years olds The mass was removed surgically and histology showed a cystic wall, squamous epithelium mature adipose tissue, calcifications, pilosebaceus units, nervous tissue and some mature Glands.
Conclusions: Ovarian masses are infrequent in children but they should be considered in patients with abdominal pain chronic. Some be associated with precocious puberty, main in these case not.

P3-d1-1428 Puberty and Gonads 9

Primary ovarian failure and a successful pregnancy

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Introduction: Primary ovarian failure results in most cases from chromosomal abnormalities. Rarely it's acquired.
Case study: We present a woman, aged 25, observed for the first time with 16,986 years, referred for short stature and primary amenorrhea.
She had adrenarche when she was 15 years old, but no breast development. She was born from a healthy pregnancy, delivered at term, with weight 3850 g, and had a normal psychomotor development and good learning. She was submitted to an auto-transplant at 4 years old for an Acute Lymphoblastic Leukaemia, with remission. At first appointment: Height 148,7 cm (-2,14 SD); Weight 47 kg (-0,93 SD). Phenotypically she had some characteristics suggesting Turner's Syndrome: webbed neck, low-set ears, cubitus valgus, widely spaced nipples and parcial syndactily of left feet's 2nd and 3rd fingers. Tanner stage was P3M1. The laboratory workout revealed a hypergonadotropic hypogonadism: FSH 101 mUI/ml; LH 16,1 mUI/ml and estradiol < 9 pg/ml. Peripheral blood and cutaneous fibroblasts karyotype was 46,XX. Uterus and ovaries haven't been identified on pelvic ultrasound and pelvic CT identified a small and atrophic uterus, the ovaries had regular morphology but were undeveloped for the age group.
We admitted gonadal disgenesia XX as the most probable diagnosis and started estrogenic therapy and after that combined therapy with estroprogestative, with menses. Four years after the diagnosis the patient was again concerned about fertility and another pelvic ultrasound was carried out, showing now uterus and ovaries with normal size according the expected for age. Two years later the patient got pregnant without medical aid and gave birth to a healthy boy.
Conclusion: Another possible diagnosis is primary ovarian failure due to therapy for LLA with late ovarian recovery. There are reports of similar cases, but it is unusual the recovery of ovarian function so many years after castration by therapy for malignant disease.

P3-d1-1429 Puberty and Gonads 9

Premature ovarian failure: management in adolescents

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Background: Premature Ovarian Failure (POF) in adolescent is increasingly becoming common. The autoimmune spectrum, traditionally thought to be 30% is probably increasing. The ever expanding molecular biology field probably will probably reduce the incidence of Idiopathic POF. We report 3 cases of POF, requiring multiple professional involvement.
Case 1: 17 years presented with primary amenorrhea. Her BMI was 17.5, Breast development was Tanner 2 to 3. Elevated Follicle stimulating hormone (FSH; 93 U/L) and Luteinising hormone(LH; 35 U/L) Her Oestradiol was low at less than 37 pmol/L, Thyroid stimulating hormone (TSH), prolactin, normal testosterone levels and normal female karyotype. Magnetic resonance investigation (MRI) of pelvis showed small pre-pubertal uterus. No definite ovaries were seen. She was started on hormone replacement therapy and being monitored.
Case report 2: Patient had menarche at the age of 12 and had a regular menstrual cycle thereafter with periods which were not heavy. Periods stopped about 18 months later. She also complained of flushes, mood swings. Her BMI was 19.
Investigations revealed raised gonadotrophins suggestive of premature ovarian failure with low oestradiol, FSH-107 U/L, LF-26U/L, Ostradiol 24pmol/l, Normal Female karyotype, auto-nuclear antibody screen, thyroid function test and bone densitometry. She was commenced on the contraceptive pill.
Case 3: Patient referred for delayed puberty. Investigations suggested Coeliac disease confirmed on Biopsy. She had high gonadotrophins, prepubertal Uterus on MRI, Negative ovarian antibodies. She has been commenced on estrogen therapy and is steadily progressing in puberty.
Management of patients with POF requires close interaction of Paediatric

Endocrinology service with Gynaecologists, especially with later management of patients on hormone replacement therapy and also to discuss emerging evidence of fertility techniques.

P3-d1-1430 Puberty and Gonads 9

Testosterone level and response to HCG stimulation in children with micropenis

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Background: Testosterone plays a crucial role in male sex differentiation. Masculinization, penile length and prostrate are primarily due to action of 5HDT produce from testosterone
Objective and hypotheses: To determine baseline testosterone level and response to HCG stimulation in prepubertal children with micropenis.
Methods: All children with micropenis seen in an endocrine clinic over a six months peroid who had an HCG stimulation. Information retrieved from case records.
Results: Eight children seen over study peroid with age range 0 - 11 years and mean age of 55.66 months. Mean penile length was 2.06cm. . all six of eight children who had HCG stimulation, responded positively with increase in testosterone level and all four treated with testosterone responded with increase in stretched penile length.
Conclusions: Positive response of testosterone in all children after HCG stimulation and an increase in stretched penile length after treatment with testosterone.

P3-d1-1431 Puberty and Gonads 9

Premature adrenarche: long-term implications

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Background: Idiopathic premature adrenarche (IPA) has been considered an extreme of normal variation. Areas of controversy include the question whether IPA in girls is associated with a higher rate of progression to the polycystic ovary syndrome (PCOS) and whether LBW increases the risk of developing IPA.
The aim is to evaluate young women with a history of IPA for the regularity of menstrual cycle, presence of PCOS, and obesity. Furthermore to assess the prevalence of history of SGA and the prevalence of overweight and obesity in this group of patients at presentation.
Patients and methods: 68 young women who were investigated during childhood for PA were contacted and answered a semi-structured questionnaire, regarding age of menarche, regularity of menses, presence of persistent acne, and hirsutism, pelvic sonographic evaluation and report of Ht and Wt. Hospital records were reviewed for BW, Ht and Wt at diagnosis, DHEAS levels, results of ACTH test, maternal age at menarche and maternal history of PCOS. Patients with NC CAH were excluded.
Results: History of SGA was present at 10.2 %. Positive maternal history for PCO was present at 22 % of cases. At diagnosis age was 7.8 yrs ± 0.9 , BMI 18.6 ± 2.7 , 44% were overweight and 19% were obese.At F/U age was 16.8 yrs ± 2.6 , BMI 19.1 ± 3.7 , 6.5 % were overweight and 0 % were obese. 14.7 % had clinical syndrome of PCO.
Mean maternal age at menarche was 12.8 yrs ± 1.5 and age of menarche of the girls 12.2 yrs ± 1.1
Conclusions: Data from this patients cohort implicate that the majority of girls with IPA are overweight or obese. History of SGA was encountered only in 10 % of the patients. Age at menarche did not differ significantly from that of the mothers. At follow-up (post-menarche), although BMI was WNL in the majority of young women, PCOS was present in 15 % of this cohort. Further follow-up of the patients is needed to clarify the link between early androgen excess, PCOS and metabolic complications.

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Effects of nourishing "Yin"-removing "Fire" Chinese herbs on the gene translation of hypothalamic ghrelin and its receptor in female precocious rats

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Background: Chinese Herbal Mixture has been used in treating precocious puberty since 1980s in China.The related mechanism is not very clear. Ghrelin plays an important role between the HPG axis and energy homeostasis during puberty onset.
Objective and hypotheses: To investigate the effect of Chinese herbs on the hypothalamic ghrelin/GHS-R1a genes expression during puberty onset in Female precocious rats
Methods: 40 female SD rats aged 3 days were divided randomly into normal (N), model(M) , H (models fed with Chinese herbs) and S (models fed with saline)groups, 10 rats within each group. All rats except those in Ns were subcutaneously injected with 300μg danazol to induce precocious puberty on postnatal day5. From P15, animals in H and S were administered with Chinese Herbs and normal saline respectively for every day. The vulvas opening in 4 groups were observed every day from P20. Rats in M were killed as soon as their vulva opened, with the same number at each group simultaneously. the hypothalamic ghrelin and GHS-R1a mRNA were measured by real-time PCR, and by radioimmunoassay for sexual hormones and hypothalamic GnRH .
Results: The vulvas opening in Ms and Ss was between P21and P23, earlier than those in Hs and Ns. Blood levels of E_2, LH, hypothalamic GnRH and uterus organ coefficient in Hs and Ns were statistically lower than those in M and S ($P< 0.05$). and the rats in H group possessed a smaller ovary organ index in contrast to those in S group and N group. There were declines in the levels of hypothalamic ghrelin and GHSR1-α mRNA in M group and S group in comparison to those in the Ns ($P< 0.01$), however, the levels of hypothalamic ghrelin and GHS-R1a mRNA in H were statistically higher than those in M and S group ($P< 0.01$).
Conclusions: Rats exposed to danazol on on P5 exhibited an increased gene transcription of hypothalamic ghrelin and GHS-R1a at puberty onset, and the Chinese Herbs up-regulated the gene transcription of hypothalamic ghrelin and GHS-R1a.

P3-d2-1433 Puberty and Gonads 10

Precocious puberty in a familial type 1 neurofibromatosis case caused by a microdeletion on chromosome 17q11.2

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Background: Type 1 Neurofibromatosis (NF-1) is a genetic multisystemic autosomal dominant disorder (frequency: 1/3000), with highly heterogeneous clinical symptoms (café au lait skin spots, plexiform neurofibromas, optic glyomas, freckling of the axillae or inguinal regions, Lisch nodules in the iris, musculoskeletal abnormalities). In 80-90% of cases NF-1 is caused by punctiform mutations of NF1 gene (Neurofibromin) whereas almost 5% of cases show complete deletion of NF1, correlated with a peculiar phenotype.
Case description: D.D came to our observation for language delay, craniofacial dysmorphisms, pigmented cutaneuos spots, precocious puberty. At first clinical observation: weight and height above the 90th percentile, macrocrania, dysmorphic facial features, gigantism, multiple cafè au lait skin spots (>10), neurofibromas (3), melanocytic nevus in the abdominal region. Moderate cognitive delay, hyperactivity, attention deficit, bone age older than chronological age, normal cardiac and ocular functions. Brain NMR: hyperintense white-matter lesions bilaterally located in thalamus and cerebellum, pituitary gland slightly bigger than normal. Spinal NMR: multiple plexifrom neurofibromas. Genetic analysis (standard karyotype, research for punctiform NF1 gene mutations using PCR, DHPLC and direct DNA sequencing) were

negative. MLPA analysis identified the deletion of the entire NF1 gene in both D.D. and her mother (whose examination revealed macrocrania, gigantism and cognitive delay). Array CGH (Comparative Genomic Hybridization) documented a deletion of 1,4 Mb in 17q11.2 including OMIM NF1 gene, RNF135, SUZ12 and confirmed the diagnostic hypothesis of a familiar autosomal dominant case.
Conclusions: Precocious puberty was one of the first symptoms appearing in our patient. The 17q11.2 microdeletion described in our family correlates with a serious clinical presentation and higher risk of malignant peripheral nerve tumors.

P3-d2-1434 Puberty and Gonads 10

Korean environmental health survey (KorEHS) in children and adolescents focusing on puberty

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Background: Nowadays, there is tendency that the puberty develops earlier. Several reports indicate that there might be an association between the environment and the precocious puberty.
Objective and hypotheses: We designed the study to evaluate the onset age of puberty in Korean children and adolescents and to analyze the association between the environmental factors and the precocious puberty.
Methods: We designed the Korean environmental health survey (KorEHS) in children and adolescents as the pilot study based on the school unit for 6-19 years. Pubertal status was examined by self report using the standardized figures of Tanner stage. Testis size was measured by self manual examinations. Selected exposure biomarkers, i.e., lead, mercury, cadmium in blood and bisphenol A (BPA), 2 diethylhexyl phthalate (DEHP) metabolites and 1 di-n-butyl phthalate (DBP) metabolite, cotinine and creatinine in spot urine were analyzed in 351 pilot subjects from elementary, middle, and high schools of two cities.
Results: The mean age of breast budding in females was 10.05 (7.75~13.33) years and the mean age of puberty onset (4mL of testis volume) in males was 11.67 (8.80~13.43) years. When we compared the levels of exposure biomarkers in male children (< 9 years of age) subdivided by testis volume, the metabolite of DEHP was higher in the male children with precocious puberty ($p < 0.043$).
Conclusions: The mean age of puberty onset based on breast budding or testis size was yonger than the previous report. The environmental factors might be involved in the development of precocious puberty, therefore more study including larger populations will be required.

P3-d2-1435 Puberty and Gonads 10

Hyperandrogenism and aggression; assessment of anxiety - anger scale in the polycystic ovarian syndrome cases

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Background: There are contradictious results about relation between androgens and aggresivity. In this study it is aimed to observe anxiety and anger in girl adolescents with the most frequent cause of hyperandrogenism, polycystic ovary syndrome and compared with adolescents with measured anger levels in order to learn effects of increasing androgen levels.
Material and methods: 23 adolescents between ages 12-18 with serious cases such as. Symptoms of hyperandrogenism: menstrual ırregularity, acne, hirsutismus and overweight-obesity were included in this study. Ferriman-Gallway scoring method is used to hirsutismus level. Blood samples were collected from adolescents in order to get a view on biochemical and hormonal evaluation. All cases were performed pelvic ultrasonography and anxiety-anger scale tests (***Anxiety and Anger Inventory, State and Trait Anxiety Inventory, StateTrait-Anger Expression Inventory***).
Results: The results show that the scores of anger and worrrying of PCOS group is significantly high compared to the control groups scores.In the PCOS group level of the state and trait anxiety inventory and anger control score are in an inverse ratio.
Conclusion: It is noticed that when individuals from group PCOS feel worried they are unable to control their anger, thus they get angry easier. It is also spotted that they have more explosion of wrath than the control group.

P3-d2-1436 Puberty and Gonads 10

Clinical features of Kallmann syndrome and the importance of smell test(s) and brain magnetic resonance imaging in diagnosis: report of five adolescents

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Background: Kallmann syndrome is a genetic disorder with the hallmarks of anosmia and hypogonadotrophic hypogonadism. Kallmann syndrome is diagnosed when low serum gonadotropins and gonadal steroids are coupled with a compromised sense of smell. The hyposmia/anosmia can be evaluated by subjective smell tests; however the use of objective tests is more reliable because of the low sensitivity of subjective tests.
Objective: To present the clinical and laboratory features of five male adolescents diagnosed with Kallmann syndrome.
Methods: LHRH test was performed in all of the patients. An olfactometer was used for the assessment of olfaction. Two different odors were used in olfactometry testing; Carbondioxyde as a trigeminal stimulant and 2-phenyl ethyl-alcohol as a pure olfactory stimulant. An EEG record was also performed synchronously with olfactometry testing. Sniffin' Sticks Test were performed to assess subjective smell function of patients. The score is expressed as TDI (threshold, discrimination, identification) value, where values below 16 points denote functional anosmia and values above 30 points represent normosmia. The scores in between are considered to reflect hyposmia.
Results: All patients presented with short penile length and/or delayed sexual development. Basal and stimulated gonadotropin levels were consistent with hypogonadotropic hypogonadism. Results of the EEG-olfactometry analysis showed that, while there was no brain responses to pure olfactory stimuli in any of the patients, brain responses to trigeminal stimuli were observed in all patients. Sniffin' Sticks Test revealed anosmia in four patients and hyposmia in one patient. Brain MRI showed bilateral agenesis of the olfactory bulbs and the EEG olfactometry analysis revealed anosmia.

Conclusions: We emphasize the importance of both subjective-objective smell tests and cranial MRI findings in the diagnosis of Kallmann syndrome.

P3-d2-1437 Puberty and Gonads 10

The evaluation of GnRH analog treatment on anterior hypophysis hormones in girls with central precocious puberty

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Background: There is still no comprehensive study performed in childhood about the effects of GnRH analogs which are used for a long time in central precocıous puberty treatment on hypophysis hormones except gonadotropins.
Objective and hypotheses: This study aimed to investigate the effects of GnRHa treatment on anterior hypophysis hormones in girls with central precocıous puberty (CPP).
Methods: The study included 62 girls with CPP who received GnRHa treatment (Leuprolide asetat, Lucrin depot®, 3,75 mg intramuscular or subcutaneusly in every 28 days) for at least 6 months. All the patients underwent serum ACTH, cortisol, TSH, fT3, fT4, IGF-1 and IGFBP-3, prolactin (PRL) (3 blood samples in every 15 minutes) measurements before and during teratmen,in every 3 months added to clinical assesment.
Results: The initial age for the treatment was 7,9±1,3 (4,3-10) and the bone-age was 9,5±1,9 (4,1-12). Prolactin levels were increased in first 9 months of GnRHa treatment according to initial levels, but only the elevation in third months was statically significant. Although only 2 patients (3,2%) had hyperprolactinemia initially, 11 other patients (17,7%) developed hyperprolactinemia in different periods of treatment. It is observed that GnRHa treatment did not effect TSH secretion, but decreased fT3 levels, increased fT4 levels after 9th month of treatment.GnRHa found to decrease ACTH secretion in 6th and 15th months, but not under normal values, and did not effect cortisol levels. After the 6th month of the therapy IGF-1 levels found to be increased and IGFBP-3 decreased.
Conclusions: We suggest that PRL levels should be controlled during follow up in patients treated with GnRHa.

P3-d2-1438 Puberty and Gonads 10

Central precocious puberty and hypobetalipoproteinaemia in a boy with Prader-Willi syndrome

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Background: Prader Willi syndrome (PWS) is characterized by neonatal hypotonia, obesity, short stature and usually associated with growth hormone deficiency, delayed puberty and hypogonadism.Only a few cases of precocious puberty have been reported.
Objective and hypotheses: We describe a case of a 9 years old PWS boy with maternal disomy who presented with precocious puberty.
Method: His height was 134.5cm (HSDS : 0.25), BMISDS: 1.61, pubic hair (PH) 2 and testes 5ml. He had increased height velocity (7.5cm/year), and pubertal response to GnRH test. His bone age was advanced at 13 years. He also presented low levels of cholesterol, triglycerides and apoB, suggesting heterozygous hypobetalipoproteinemia. The above diagnosis was supported by family lipid history Pituitary MRI was normal, Neurological, ophthalmological examination, echocardiogram and ultrasound of liver were normal.
Results: LHRH analogue therapy was started, which suppressed pubertal development. The patient will be reevaluated for growth hormone therapy.
Conclusions: To our knowledge this is the fifth male patient with genetically confirmed PWS and precocious puberty and the first with coexistence of hypolipidemia.

P3-d2-1439 Puberty and Gonads 10

Puberty in obese and overweight boys and adolescents 10- and 15-years-old in YUSAD study

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Background: Secular trend of earlier onset of puberty in age reflects better health and nutrition.
Objective and hypotheses: Determining the stage of development puberety in boys at the age of 10 years and the at the age of 15 compared to the level of BMI. The research was done in the Yugoslav study of atherosclerosis precursors in school children (YUSAD) based tracking.
Methods: Data were obtained by physical examination and evaluation stages of development puberty. (standards Tanner).
Respondents were of the third grade (1360) primary schools (PS) and the same student in the eighth grade. Primary school in six health centers.All subjects were classified according to BMI into three groups: I-thinnes, II-III and normal weight and obese-overweight. Statistical significance was tested by X2 test.
Results: At the age of 10 years to assess the size and design of the external genitalia in the first stage of development was in all three groups of boys 67-69%, in the second stage I / II / III group-32% / 29% / 29%. Prior to the appearance and development of pubic hair in the first stage of development was in all three groups of 71-77%% of boys, in the second stage I / II / III group-21% / 24% / 26%. At the age of 15 years to assess the size and design of the external genitalia in Ii II stage of development was I / II / III group-20% / 4.5% / 12.6%, in the third stage I / II / III-26 %group, 9% / 18.5 / 19.26% while the fourth and fifth stages of development had I / II / III group-52% / 75% / 67%. At the age of 15 years to design and development of pubic hair the first and second stages of development was I / II / III group-23% / 7.8% / 13.3%., in the third stage I / II / III group-28% / 15 , 9% / 12.2%, while the fourth and fifth stages of development had I / II / III group-47% / 76% / 73%.
Conclusions: No difference development puberety in boys between obese and normal weight adolescents.

P3-d2-1440 Puberty and Gonads 10

An unusual case of bilateral galactocele in a male infant

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Background: Galactocele is a rare, benign, milk-filled cystic lesion of the mammary gland that generally occurs in young women during or after lactation. Galactocele is a very rare cause of breast enlargement in infants and children. In this paper we describe the case of a male infant with bilateral galactocele without hyperprolactinemia.
Case report: An 6-month-old boy referred to our clinic with a 4-month history of progressive bilateral gynecomastia and no other relevant history. The child was otherwise well and thriving. On physical examination, he had bilateral breasts Tanner stage 3 and both breasts felt cystic upon palpation with no nipple discharge, and bilateral testes were 2 ml. The rest of the examination was normal. Levels of serum prolactin were 9,05 ng/ml (N: 4.04-15.2), free thyroxine 1,42 ng/dl, thyrotropine 2.08 uIU/ml, FSH: 0.76 mIU/ml, LH: 0.76 mIU/ml, total testosteron 0.03 ng/ml, and cortisol 7.35 µg/dl. Electrolytes, alanine transaminase, and lactate dehydrogenase values were normal. Ultrasound imaging showed fluid filled cystic collections within both breasts. Repeated serum prolactin levels were also normal. A normal 46 XY karyotype was present. Magnetic resonance imaging of the brain and the pituitary region were normal. At 12 months breast appeared enlarged and the diagnosis of bilateral galactocoele was confirmed following surgical excision. The child had a benign recovery and remains asymptomatic 6 months after surgical excision with no evidence of recurrence.

Conclusions: Hyperprolactinanemia was not established in our case. The etiology is stil unknown but it has been suggested that it may be associated with previous or present stimulation by prolactin, some form of ductal obstruction or the presence of secretary breast epithelium. Although rare, galactoceles should be considered in the differential diagnosis of breast enlargement in infancy.

P3-d2-1441 Puberty and Gonads 10

Hormonal and metabolic evaluation of adolescents and young adult women assisted since childhood due to premature adrenarche

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Background: Idiopathic premature pubarche (IPP) is the presence of pubic hair before 8 years old in girls and 9 in boys. Considered as "normal variant", probably result of increased sensitivity to adrenal androgens in peripubertal period, refered to as precocious adrenarche (PA). Follow up studies have related higher prevalence of metabolic syndrome, hirsutism, acne and polycystic ovaries to PA.
Objective and hypotheses: Evaluate patients assisted in childhood due to PA, in order to disclose metabolic and hormonal dysfunctions.
Methods: 84 females patients with previous PA were called, 27 attended and agreed upon clinical, anthropometric and hormonal reassessment.
Results: They were between 12 and 28 years old (median: 17yrs); 8 (29.6%) were overweight/obese, 11(40.7%) had acne, 14(51.8%) hirsutism, 3(11%) acanthosis nigricans, and all had normal blood pressure.
No patients had fasting glucose and HbA1c altered nor hyperinsulinism, 5(18.5%) had low HDL concentrations. Hormone values were expressed as median (minimum/maximum). LH/FSH: 0.7 (0.004-2.3); estradiol: 4.9pg/mL (20.0-24.4); androstenedione: 2ng/mL (1.4-4.0); 17-OH-progesterone: 163.5ng/dL (62.0-510.0); testosterone: 35.0ng/dL (16.5-68.7) and DHEA-S: 255.3mcg/dL (153.3-440.0).
Conclusions: In this study we observed the evolutionary spectrum of PA, ranging from normal to clinical and biochemical hyperandrogenism. Overweight/obesity in 29.6%, even without dysglycemia and dyslipidemia, indicates the need to alert patients to prevent these complications.

P3-d2-1442 Puberty and Gonads 10

Williams and Beuren syndrome: what about endocrine associations? About 2 cases

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Background: Williams and Beuren Syndrome (WBS) is a rare genetic disease due to a chromosomal microdeletion in 7q11.23.Clinical phenotype is widely heterogeous in severity and manifestations.This syndrome often associates a characteristic facial dysmorphism, cardiovascular abnormalities and a specific neuropsychological profile.Endocrine manifestations are more rare and must be looked for systematically.
Objective and hypotheses: To highlight a rare disease which can affect both girls and boys so as to emphasize its specific clinical characteristics and its possible association with endocrine abnormalities.
Methods: We report the case of a 7-year-old girl and a 4-year and 10 month old boy. The girl went at first time for a psychomotor retardation history and permanent constipation.The boy consulted at the age of 4 for a limping.Both of them had a facial dysmorphism.
Results: On examination, the girl has a small mental retardation.She had a lumbar lordosis and a facial dysmorphism with a large forehead, a nose with bulbous end,full cheeks,wide mouth with everted lower lip realizing a "facies' elf".She has a peripheral hypothyroidism and a precocious puberty which was particularly difficult to manage as she has a child behaviour.She received a thyroid hormone replacement therapy and suppressive treatment of puberty. Menstruation disappeared which was psychologically helpfull. The boy went for lameness.
On examination, he has a triangular-shaped face with epicanthus and pulpy lips with open mouth. Its behaviour was characteristic. On cardiac auscultation, we notice a systolic murmur due to a supra-valvular aortic stenosis. Thyroid balance was normal.He has no signs of precocious puberty.None of the two children has a growth retardation. Microdeletion in 7q11.23 was found in both cases.
Conclusions: Prevalence of WBS is 1/7500 to 1/20 000. It is due to a de novo mutation. Its characteristics must be known so as to look for its rare associations and particularly endocrine ones.

P3-d2-1443 Puberty and Gonads 10

Pseudocyesis as a cause of abdomen enlargement in a female adolescent

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Background: Pseudocyesis is a rare condition in the pediatric population characterized by all signs and symptoms of pregnancy except the existence of a fetus. In some patients it is associated with organic etiology, in others with mental disorders, but it also occurs in those without disorders in their medical history.
Pseudocyesis occurs in both sexes, but more frequently in women. An effective treatment is a combination of psychotherapy and pharmacotherapy with antidepressants and antipsychotics.
Objective and hypotheses: We present a 15,9-year old girl with pseudocyesis as a cause of abdomen enlargement, who comes from an ordinary family with a negative history of psychiatric illness.
Method: A 15,9-year old female patient was admitted at the Department of Pediatrics, Split, Croatia, due to an abdominal distension of unknown cause. Eight months before admission she had her first and only sexual intercourse. The organic etiology of her condition was excluded, since all diagnostic tests were within reference values.
Results: As the psychiatric evaluation of our patient showed her condition being caused by underlying depression, she started to take an antidepressant, leading to a simulated labor after a month of therapy (ninth month of pregnancy), and the belly eventually withdrew.
Conclusions: Pseudocyesis is a condition in which a non-pregnant persons believe that they are pregnant, with the presence of all objective signs of pregnancy except the existence of the fetus. Almost all the symptoms of pseudocyesis were seen in our patient. Laboratory and image findings were within the reference values, therefore excluding hormonal changes as a cause of her condition.
As the psychiatric evaluation of our patient showed her condition being caused by underlying depression she started to take an antidepressant, leading to a simulated labor after a month of therapy, and thus resolving her condition.

P3-d3-1444 Puberty and Gonads 11

Prevalence of genital abnormalities among Uzbek boys in Tashkent city

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Background: International studies from the late 20th century have raised concern about a rising prevalence of congenital genital abnormalities in boys, with some suggesting that environmental endocrine disrupters may be a factor.
Objective and hypotheses: The purpose of the study was to evaluate the frequency of genital abnormalities in Uzbek children and teenagers of Tashkent city.
Methods: We examined 818 boys aged from 7 to 18 years, the study was conducted between 2009 and 2011.
Boys were examined in 3 urban districts of Tashkent city i.e. (Mirzo-Ulugbek, Shakhantaur, Yunus-Abad). Micropenis was established as a SPL 2.5 standard deviations less than the mean for age group.
Results: The mean age of boys was 12.5 years. We revealed micropenis in 30 boys (3.6%), cryptorchidism in 16 (1.95%) and varicocele in 6 boys (0.7%). These abnormalities were associated with overweight, short stature, pubertal delay or underweight.

Conclusions: We obtained relatively high frequency of micropenis among Uzbek boys in Tashkent city. There were associations with endocrinopathies.

P3-d3-1445 Puberty and Gonads 11

Pubertal disorders by acceleration: behavior in a population during the period from January 2010 to January 2012

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Background: Disorders by acceleration are affecting children with increased frequency. There is few data on their frequency, age of onset, symptoms or etiology.
Objective: Describe the most common pubertal disorders by acceleration, in patients attending the Pediatric Endocrinology clinic from January 2010 to 2012.
Method: Cross sectional retrospective study, including patients attending the outpatient pediatric endocrinology service from January 2010 to January 2012. We evaluated clinical and demographic variables. For quantitative variable measures of central tendency and dispersion were calculated. For categorical variables proportions and frequencies were used. The association analysis of categorical variables was performed using chi-square and a P value less than 0.05 as statistically significant.
Results: 594 charts were identified in the database, 89 were excluded for loss of follow up. 505 charts were analyzed, female predominance was found 95.3% (482 pts), the average age of onset was 7 years (95% CI 6.84-7.21). The most common initial symptom was breast development < 8 years in 50% (253 pts) followed by pubic hair < 8 years in 17.8% (90 pts.). 60.7% patients received pharmacological treatment with LhRh analogs. Bivariate analysis was performed to determine the opportunity for pharmacological management in the first 6 months after diagnosis, it was found to be statistically significant ($p = 0.009$). The most common etiology was idiopathic in 70.2%. Obesity was present in 24.3%, the most frequent diagnosis was precocious puberty by 54.9%.
Conclusions: Pubertal disorders by acceleration are part of a spectrum of endocrine diseases that among other outcomes, may affect the final height of the patient. It is relevant to understand the behavior of these disorders and their possible causes. Our results are consistent with the literature, their presentation is more frequent in females with idiopathic etiology, but obesity is present with a high frequency.

P3-d3-1446 Puberty and Gonads 11

Sexual development following exposure to topical testosterone during prepubertal age: a case report

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Background: Exposure to topical androgen preparation is a rare cause of virilization in young children. Several case reports have documented partial or full regression of virilization after discontinuation of exogenous androgen exposure and speculate the long-term consequences of early puberty, reduced final height, and psychosocial distress. Central precocious puberty (CPP) secondary to androgen excess have been described in patients with congenital adrenal hyperplasia (CAH). However, no known cases document the development of CPP in children inadvertently exposed to sex steroids.
Case description: A 3.5 year-old girl referred for evaluation of pubic hair growth and clitoromegaly. On exam: height and weight 95%, facial comedones, husky voice, breast Tanner 1, pubic hair Tanner 2, enlarged clitoris.
Results: Testosterone 192 ng/dl, prepubertal17-OH-progesterone, DHEAS, LH, FSH. Brain MRI and pelvic ultrasound unremarkable. Bone age advanced 2 years.
Follow-up: The father admitted to using testosterone gel daily for 2 years. The father stopped using testosterone. After 1 year the patient's acne, pubic hair resolved and growth velocity returned to prepubertal range. At 7.5 years the patient started developing pubic hair and breast to Tanner 2-3. Height velocity increased to 95%, bone age advanced to 12.5 years. GnRH therapy was initiated and 4 months later breast and pubic hair regressed, and height velocity decreased to 50% for age.
Conclusions: The patient's long-term experience highlights the importance of education and prevention regarding use of topical androgens in households with young children. Prolonged exposures may lead to increased risk for CPP even several years after withdrawal. Patients' growth, pubertal stage and bone age should be monitored with regular follow-up.

P3-d3-1447 Puberty and Gonads 11

Aromatase excess syndrome (AEXS) in a family from Santo Domingo, Dominican Republic

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Background: AEXS also called Prepuberal Hereditary Gynecomastia or Familiar Hiperestrogenism has been documented in males and female and is due to a genetic alteration with autosomic dominant hereditary trait.
We present 3 affected brothers in 2 families with the same father.
Cases reports:
Case YR: Age:17 years old; Height: 154 cm; Weight: 49 kg.; Genitalia: Normal; Tanner V Mammary , pubic hair IV; Testicular vol 12 ; Estradiol: 40.6 ng/Dl; Total Estrogen: 118 ng/Dl; Total Testosterone: 338 ng/ml; FSH 3.2 mIU/ml .LH 2.3 mIU/ml
Case AR: Age:12 years old; Height: 139 cm; Weight: 39 kg.; Genitalia: Normal; Mammary Tanner V .Pubic III; Testicular volume 10; Estradiol: 45 ng/Dl; Total Estrogen: 105 ng/Dl; Total Testosterone: 250 ng/ml; FSH 4.6 mIU/ml .LH 3.8 mIU/ml
Case GR: Age:10 years old; Height: 143 cm; Weight: 37 kg.; Genitalia: Normal; Pubic Tanner II, Mammary Tanner IV; Testicular Vol 5; Estradiol: 39 ng/Dl; Total Estrogen: 96 ng/Dl
Total Testosterone: 18 ng/ml; FSH 4.3 mIU/ml .LH 2.5 mIU/ml
Father: Normal phenotype, short stature: 143cm
Mother: 161cm (mother of AR and GR)
Discussion: The excess of conversion from testosterone to estrogen by aromatase excess produced in our cases important gynecomastia which was the principal reason to get medical assistance for psychological reasons in males. This is a pattern of hipogonadism hipogonadotropic by estrogen excess, but the genitalia development were not affected despite high estrogen levels and low testosterone as typical in AESX .The molecular analysis in these cases made with Drs. Fukami and Ogata assistance in Japan, did not differ with the reported altered gene cytocrome P450 ,Family 19 ,Subfamily A, Polypeptide 1 ,CYP19A1.

P3-d3-1448 Puberty and Gonads 11

Central precocious puberty due to hamartoma

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Background: During the first year of life it might be difficult to differ between central or pseudo precocious puberty or just transmission of maternal estrogens.
Case report: We report about a 4 months old female infant with premature thelarche and vaginal efflux. In the meantime, the size of the mammary corpus war regressive, however, at the age of 7 months, she developed vaginal bleedings together with a marked increase of the mammary corpus size. The LHRH stimulation showed pubertal values with higher LH than FSH levels and high estrogen levels. The MRI revealed a 7mm hamartoma type IIa according to Valdueza. Therefore, a therapy with Leuprorelin has been initiated leading to regression of the signs of precocious puberty.
Conclusions: A fluctuating progress of puberty also with partial remission does not exclude a central hamartoma. A neurosurgical removal of the hamartoma is planed. The medication with leuprorelin seems to be successful.

P3-d3-1449 Puberty and Gonads 11

Virginal breast hypertrophy in a 12-year-old girl: a case report

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Background: Virginal breast hypertrophy (juvenile gigantomastia) is a benign disorder of the breast in which one or both of the breasts undergo a massive increase in size during adolescence. We present a case of virginal breast hypertrophy that is a rare condition in the paediatric age group.
Case report: An 12-year-old girl presented with a 6-month history of onset of puberty with rapid growth of breast. Although her parents thought that pubertal progress was normal for the first four months, in last two months, her breasts had enlarged progressively with associated mastalgia, back and shoulder pain, resulting in a slouched posture and requiring antibiotics for superficial skin infection. There was no family history of any similar disorder and no history of breast disease or ingestion of oestrogens. Her height was 149 cm (10-25th centile) and weight 47 kg (25-50th centile). Her bilateral engorged breasts were indurated, dehiscenced, very tender with prominent superficial venous dilatations. Laboratory investigation was normal including prolactin, thyroid functions, tumour markers of α-fetoprotein, βHCG, and serum CEA. It was planned surgical reduction mammoplasty and PTEN mutation analysis.
Conclusions: In patients with virginal breast hypertrophy, the physical deformation is not only psychologically intimidating, it can also lead to severe orthopedic problems and ulcerative breast infections. Therefore, juvenile gigantomastia is not just an exceptional variation of breast shape and size, it is rather a disease of considerable pathologic significance that demands sufficient surgical treatment. The complexity of this condition illustrates the need for a multidisciplinary team working in concert. The primary aim of treatment is to stabilise breast growth.

P3-d3-1450 Puberty and Gonads 11

Congenital intracranial arachnoid cysts and endocrinological outcomes in a young girl

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Introduction: Arachnoid cysts are mainly manifested with the consequent neurological disorders and it is very little information concerning their involvement in endocrinological disorders. We report a case with precocious puberty and bilateral breast fibroadenoma due to suprasellar archnoidal cyst .
Case presentation: A 8 years old girl was admitted to the hospital for evaluation of aggressive breast development. The height, 145 cm, and the weight 43 kg, exceed two Standar deviations. She had a huge breast development with bilateral fibroadenoma. The bone age was 15 years. Endocrinological examination showed that serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and estradiol had increased for her age, to levels equivalent to those for females at puberty. The levels of cortisol, thyroid hormones and prolactin were normal. An LH-RH test revealed an excessive LH reaction. There were no definite neurological deficits. CT and MRI demonstrated the presence of a large arachnoid cyst involving the suprasellar region and bilateral breast fiboradenoma.
Conclusions: In pediatric patients with arachnoid cysts, endocrinological follow-up is crucial to confirm pubertal and growth status. If the diagnose of precocious puberty will be in time it can prevent other malformations like breast fibroadenoma.

P3-d3-1451 Puberty and Gonads 11

Precipitous puberty: pathologic correlations with disturbed ovarian function

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Background: Precipitate puberty is a disorder of the sexualization process.
Objective and hypotheses: The appreciation of the functional ovarian maturity in a group of girls with precipitated puberty.
Methods: Ovarian function was assessed in a group of girls with puberty precipitated (group 1) compared with a group of girls with normal puberty (group 2) according to development criteria accepted by the population of Romania. They calculated the incidence of menstrual disorders, changes in menstrual flow, presence of dysmenorrhoea/ premenstrual syndrome, breast development, serum levels of ovarian hormones, the incidence of ovarian cysts.
Results: The existence of menstrual disturbances (66.1%-group 1; 34%-group 2), duration of the menses (66.6% - group 1; 33.3% - group 2); the quantity of the menstrual flux - altered (61.3% - group 1; 36.8% - group 2), the presence of dysmenorrhea and/or premenstrual syndrome (60.4% - group 1; 39.6% - group 2), end-stage of breast development (24.7% - group 1; 75.3% - group 2), the presence of low blood levels of ovarian hormone (81.4% - group 1; 18.6% - group 2), presence of ovarian cysts (64% - group 1; 36% - group 2).
Conclusions: These observations reveal disorders of the sexualization process on girls with precipitate puberty on the grounds of a delayed functional ovarian maturity ($p < 0.001$) compared with girls with normal puberty.

P3-d1-1452 Sex Differentiation 6

A 14-year-old patient with X chromosome monosomy mosaic karyotype and male Turner phenotype

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Background: Mosaicism is condition when there are present cell lines with different chromosomal patterns.
Objective and hypotheses: We present 14-year-old boy with a history of complicated delivery (Apgar score 7-9-9, BW-3130g, BL-51cm), poor weight and height gain since first months of life, speech delay, moderate learning difficulties. Patient presented with short stature (height -3,57SD), overweight (+1SD according to height), A1/P3/G3, testes volume of 3ml, facial dysmorphism, coarctation of the aorta, hypertension, hypermetropia, retinal pigment epithelium hypertrophy(CRPEH) in fundi ("bear tracks"), mild neurosensory hearing loss, average intellectual development. Family history: colorectal cancer in grandfather.
Methods: Endocrine, imaging, genetic studies.
Results: Endocrine tests revealed normal adrenal and thyroid axes, partial growth hormone deficiency confirmed in stimulation tests, IGF-1 243 ng/ml, delayed bone age by 2 years, prepubertal LH and FSH levels in LH-RH stimulating test, 17-OHP 147ng/dl, DHEA-S 2265 ng/ml, testosterone 549 pg/ml (steroid profile in course); 24-hour-ABPM confirmed hypertension. Abdominal ultrasound was normal except of decreased blood flow in renal arteries. Echocardiogram, CT angiogram showed abnormal aortic arch with critical coarctation of the aorta and intensive collateral circulation. MRI of central nervous system appeared to be normal.
Chromosomal analysis revealed mosaic karyotype 46,X,mar[40] / 45,X [10]. ish der(Y)(wcp Y+,DYZ1+).
The patient underwent percutaneous endovascular stent implantation. He expects endoscopy of gastrointestinal tract due to association CRPEH and familial adenomatous polyposis (FAP).
Conclusions: There are possible various abnormal chromosomal mosaic patterns influencing patient's phenotype. Manifestations of X monosomy depends on random inactivation of this chromosome. In our patient, developed as male, we observe symptoms specific for Turner syndrome.

P3-d1-1453 Sex Differentiation 6

Short stature presenting with 45, X/46, XY mosaicism

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Background: Karyotype analysis is applied to exclude Turner syndrome in female children who presented with short stature but it isnot routine in boys.
Objective and hypotheses: We present a case with a boy who presented with short stature and 45, X / 46, XY karyotype mosaicism.
Methods: 13-year-old patient was presented with the complaint of short stature. At diagnosis his height SDS was -4.05. Bilateral inguinal hernia was detected. Volume of right testis was 5ml and left testis could not be palpated.
Results: Abdominal MRI showed cross ectopia. Mullerian residua or gonad were not found. Penis size was found close to the lower limit of normal values. The chromosomal analysis of the patient was reported 45,X/46,XY mosaisizm. Annual growth rate was 2 cm and we didn't observe the response to growth hormone stimulating tests. After we had diagnosed GH deficiency we started to GH threapy. In the first 5 months, we observed 3 cm height growth.
Conclusions: We suggest to perfom chromosome analysis in boys presenting with unexplained short stature and we also recommend administering GH therapy to patients who are diagnosed with a growth hormone deficiency and 45,X/46,XY mosaicism.

P3-d1-1454 Sex Differentiation 6

Profile of 46, XY DSD patients attending a tertiary care hospital: age at presentation and social background

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Background: The phenotype of the patients with DSD is varied, ranging from completely female to under virilised male. Presented here is the age profile and social background of subjects with 46, XY DSD examined in our hospital. Most of the patients with DSD are diagnosed at birth because of atypical appearance of genitalia. However some patients like those with CAIS and 5α-reductase deficiency may be missed at birth.
Objective and hypotheses: The aim of this study was to assess the age at presentation of children with 46, XY DSD attending our hospital and the social background of these patients.
Methods: Records of patients registered in the endocrine clinic of our hospital and new patients with diagnosis of 46, XY DSD were compiled. Details of age at which medical attention was sought, physical examination, chromosomal analysis, hormonal studies, psychological assessment, nature of surgery and follow up were recorded.
Results: Records of 70 patients diagnosed with 46, XY DSD were analysed. The age at which medical attention was sought ranged from few days to 23 yrs with mean age at 6.1 yrs. Twenty cases were < 1year of age, 27 cases were < 5years, 17 cases were peripubertal and 6 cases were > 20 years of age. In 20/27 cases, who were between 1 and 5 yrs of age mother noticed some atypical features and sought medical help. In the other 7/ 27 cases, doctor noticed atypical genitalia during medical examination for other incidental problems. Seventeen peripubertal cases sought medical help for lack or improper pubertal development. Forty six cases out of 70 patients were from rural area (7.5 yrs ± 7.1) and 24 cases belong to urban region (6.1 yrs ± 7.7). Six patients >20 years at presentation were all from rural area.
Conclusions: Age at presentation of DSD patients from rural areas and urban areas were comparable. However, the 6 patients who presented after age of 20 years were all from rural areas.

P3-d1-1455 Sex Differentiation 6

P.ALA65PRO mutation in a case with 5α-reductase deficiency

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Introduction: 5-α reductase deficiency is a rare form of 46,XY disorder of sexual development that occurs as a result of various mutations in the SRD5A2 gene located in the short arm of chromosome 2. In case of 5-α reductase deficiency there is inability in conversion of testosterone (T) to its more active metabolite, dihydrotestosterone (DHT). Thus, inadequate virilization of external genitalia and defective development of urethra and prostate arise in a male fetus.
Case: A seven-year-old girl presented with a swelling in inguinal region. From family history it was learnt that her father and mother was third degree relatives and her aunt had a sexual development disorder. The subject had Tanner stage 1 breast and pubic hair development, a phallus like cliteromegaly and a vaginal openning. Gonads were palpable in inguinal canals bilaterally and no uterus was found on ultrasonography. Right and left testes were visualized in inguinal canals with a size of 17x6x11 mm and 8x6x10 mm, respectively. Chromosomal analysis showed a normal male 46,XY karyotype. The subject had a FSH of 0.67 IU/ml, LH of 0.04 IU/ml and total testosterone of 0.19 ng/ml and T/DHT ratio of 16.3 which fell in a normal range. Finally, the genetic analysis of the SRD5A2 gene revealed homozygous p.Ala65Pro mutation.
Conclusion: Besides our case, p.Ala65Pro mutation was previously reported merely in one Turkish family. We believe that this mutation is common in our country where consanguineous marriages are common. Five α reductase deficiency cases having normal T/DHT ratio were reported in literature. This ratio was also slightly above the upper limit in our case. The diagnosis of 5-α reductase deficiency should be investigated by genetic analysis in cases with suspicious of this disease even with normal T/DHT ratio.

P3-d1-1456 Sex Differentiation 6

Expanding the phenotypic spectrum of the 45,X/46,XY karyotype - ovotesticular disorder of sex development (OT-DSD)

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Background: Though in literature less than 2% of OT-DSD have mosaicism with a 45,X cell line, 3 of 17 patients with OT-DSD diagnosed in our service had a 45,X/46,XY karyotype or its variants. The aim of this study was to report their clinical picture.
Case reports: All patients had normal birth weight and length and were referred due to genital ambiguity.
Case 1: Eleven-year-old girl with 2cm-phallus, single perineal opening and nonpalpable gonads, a left ovary and a right testis. Karyotype was 45,X/47,XYY. There were prepubertal levels of LH and testosterone (T) and slightly elevated FSH. She had short stature, impaired pubertal development and normal echocardiogram, abdominal ultrasound, audiometry and thyroid function.
Case 2: One-month-old infant with 1.5-cm phallus, single perineal opening, an ovotestis in the right inguinal region and an intra-abdominal left gonad (streak). Karyotype was 45,X/46,X,+mar (SRY+). FSH and LH were elevated with normal total T and low free T. The child received a female sex assignment. Echocardiography revealed pericardial effusion; abdominal ultrasound, thyroid function and audiometry were normal. She is now 7 years old and has short stature.
Case 3: Newborn with 2.2-cm phallus, penoscrotal opening, a right testis palpable in the labioscrotal fold and a left ovary inside an inguinal hernia. Karyotype was 45,X/46,XY. At 2 months old there were normal FSH, LH and T levels. The child was raised as a boy. Ultrasound showed right hydronephrosis; echocardiogram and thyroid function were normal. He is now 11 months old and has normal growth.

Conclusions: Diagnosis and classification of OT-DSD is based on histological features, but other aspects must be considered. Mosaics with a 45,X lineage may influence the choice of sex of rearing (prognosis of short stature and risk of gonadal neoplasia) and management (e.g., screening of renal and cardiac malformations and thyroid dysfunction).

P3-d1-1457 Sex Differentiation 6

Topical testosterone treatment in idiopathic micropenis

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Background: Micropenis has been defined as a penile stretched length of less than 2.5 standart deviations below the mean age. Idiopathic micropenis patients have normal hypothalamic pituitary-gonadal function and appropriate virilization at puberty.
Objective and hypotheses: We treated 59 boys between 4-9 years with idiopathic micropenis with topical testosterone esters.
Methods: All the boys had hormonal investigation and had prepubertal LHRH test responses and other causes of micropenis were excluded. Sustanon ampule 250 mg with the combination of long and short acting testosterone esters were applied transdermally twice a week(125 mg on each occasion) on Monday and Friday evenings before going to bed to the shaft of the penis excluding the glans by deep friction for 6 weeks.
Results: After 6 weeks all the patients were controlled and the stretched penis lengths were found to have increments of 2.0 +/- 0.2 cm. Their pre and post-treatment testosterone values were statistically insignificant and no bone age increment.
Conclusion: Testosterone esters friction treatment stimulates the testosterone receptors in idiopathic isolated micropenis patients and is safe to be used as the first choice of therapy instead of injection therapy which could have more side effects especially bone age increment.

P3-d1-1458 Sex Differentiation 6

Psychosexual outcomes in 3 siblings with 46, XY DSD: impact of nature versus nurture

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Background: Ambiguous genitalia results from androgen deficiency in males or androgen excess in females. Gender assignment for these children is complex as one needs to predict what the child's gender identity would be as an adult. It is a rare circumstance to assess gender identity of children with DSD who have reached aduthood without medical intervention.
Objective and hypotheses: The aim of the study was to assess for gender identity of three siblings with DSD presenting for medical examination during early adulthood.
Methods: The present study is a case report of three siblings (2 reared as male, 1 reared as a female) which was conducted in this teritiary care hospital. Data collection was done by using a detailed medical examination, medical and psychosocial history, genetic analysis and psychological evaluation. Psychological assessment tools used were: Verbal Adult Intelligence Scale,The Draw a person test, The gender identity and gender dysphoria questionnaire for adolescents and adults and The Coppersmith Self Esteem Inventory.
Results: Partial Androgen Insensitivity (PAIS) was diagnosed based on genetic and hormonal studies. IQ was $\geq$ 80 for all three siblings. None of the patients experienced any gender dysphoria. All 3 siblings had low self esteem, anxiety, immaturity and aggressive hostile tendencies. Patients reared as male showed dissatisfaction with physique, some feminine characteristics and poor social and emotional adjustment.
Conclusions: Nurture seems to exert a powerful influence in the gender identity of individuals with PAIS. Psychological distress among our patients was not due to gender dysphoria but because they found it difficult to cope with limitations placed on them by their medical condition.

P3-d1-1459 Sex Differentiation 6

46 XX DSD: ambiguity lies where?

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Background: 46 XX male generally presents with delayed puberty and normal external male genitalia. Broadly former group of patients are SRY- positive and later are SRY-negative.
Objective and hypotheses: We report a rare case of 46 XX DSD with SRY negative and without ambiguous genitalia.
Case report: 16 yr old male was brought for delayed puberty, poor testicular development and decreased libido.His Ht was 156 cm (25-50th precentile), upper segment/lower segment ratio was 0.92, vital parameters normal, SMR was: GII AIP1 (bilateral testes scrotal, 06cc). There was no gynaecomastia. Initial Gonadotrophins levels were normal and total serum testosterone (8Am) was low (195.6ng/dl). He was prescribed Inj. Testosterone @100 mg I.M/ month for 03 months However he was lost to follow up and reported after 16 months. Mean while he has gained in height of 4.7 cm and appearance of pubic hair (P 5). Gynecomastia was newly reported. Repeat FSH and LH done this time were raised (20.7 and 15.8 mIU/ml and serum testosterone was normal. karyotyping showed 46 XX chromosome and FISH revealed absence of SRY protein. MRI pelvis showed no mullerian structures. Testosterone therapy was started.
Results: SRY-positive individuals usually have normal male external genitalia, small azoospermic testes and hypergonadotropic hypogonadism .Patients with absence of SRY (SRY negative) presents with ambiguous genitalia at birth and presence of remnants of mullerian structures.. In most cases of 46XX DSD, SRY gene is translocated to the short arm- end of the paternal X chromosome which assigns in them normal male external genitalia. Molecular analysis in our patient showed absence of SRY, a rare phenomenon in 46 XX male. Our patient has gynecomastia, small testes and absence of pubertal spurt in height.
Conclusions: Absent or excessive action of other determinants within the sexual differentiation cascade are implicated in determination of male external phenotype in these group.

P3-d1-1460 Sex Differentiation 6

A rare case of 46 XX ovotesticular syndrome: delayed diagnosis

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Background: Ovotesticular syndrome is a rare sex development disorder characterized by the presence of both ovarian and testicular tissues in the same or contralateral gonad.We presented a case with signs of virilization at pubertal age and dismorphic features was diagnosed as 46 XX ovotesticular syndrome.
Case report: An fourteen year old girl admitted with the complaint of differentiation in the genital area.Her height was 145.4 cm (-2,38 SDS), weight was 48.5 kg(-0.19 SDS), Body mass index 22.94 (0,92 SDS).Breast development was tanner stage 3, there was no increased pigmentation of the genital area, pubic hair was tanner stage 3, there was no palpable gonads, phallus length was 4 cm, vaginal orifice was current and the external genitalia was consistent with the Prader stage 4. Basal hormone levels were; ACTH: 26.5 pg/ml Kortizol 19.7 mcg/dl, 17 OHP 1.11 ng/dl, DHEAS 158.8 mcg/dl, FSH 13.86 mU /ml LH 8.82 mU /ml, E2 12 pg/ml, total testosteron 90 ng/dl ,serbest testosteron 6.86 pg/ml, SHBG 9.3 nmol/l, Progesteron 1.09 ng/ml, Anti mullerian hormon 4.4 ng/ml. The stimulated testosterone response was165 ng / dl in single-dose hCG test. Bone age was 11 years .Bone radiographs were normal.Ultrasonographic examination of internal genitalia showed 28 * 24 mm hyperechoic tissue in left adnexal surgical space (over?) and no gonad or uterus in the right.Uterus was hypoplastic, fallopian tube was obstructed in genitogram. Caryotype was 46,XX, SRY(-). Laparoscopy was performed. Biopsy was taken from the tissue compatible with over and atrophic testicular tissue was removed. The extracted tissue was atrophic testicular tissue, tissue biopsy was compatible with ovarian tissue in pathology report. Patient was

considered 46, XX ovotestiküler syndrome. Female patient was scheduled for corrective surgery.
Conclusions: We want to emphasize that intersex cases may apply in the elderly and the diagnosis can easily be put in a detailed evaluation.

P3-d1-1461 Thyroid 9

A case with Graves disease who developed agranulocytosis and vasculitis during metimazole treatment

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Introduction: Methimazole (MMI) is the first choice in the treatment of Graves disease. However life threatening side effects can be seen during MMI treatment. We report a case with Graves disease who developed agranulocytosis and vasculitis during MMI treatment.
Case report: A 13-year-old girl presented with prominance eyes, irritability and palpitations. In her family history, her grandparents had hyperthyroidism and her uncle had Behçet's disease. Her weight and height were between 25-50th and 10-25th percentiles respectively. She had fine tremors, egzoftalmus and grade 2 goiter. Her blood pressure was 145/90 mmHg and pulse rate 132/min. In laboratory evaluation TSH: 0,12 uIU/ml, fT4:4,2 ng/dl, TT4:19,7 ng/dl and TSH receptor antibody 33 IU/L respectively. She was diagnosed with Graves disease and started MMI and propranolol. A month later she came with complaints of fever and sore throat. Her leukocyte and neutrophil counts were 1300/mm³ and 300/mm³ respectively. She was hospitalized and MMI was stopped. Broad-spectrum antibiotics and Lugol's iodine was started. She had cardiac arrest at 10th day of hospitalization. Her iodine treatment was stopped, and amiodarone was started for ventricular tachycardia. She had mechanical ventilation during two weeks and developed ventricular fibrilation intermitantly. During that process she was euthyroid. In her follow-up; the patient developed renal failure, plevral effusion and macular rash. Also she was diagnosed with ANCA releated vasculitis. Two days after initiation of corticosteroid acute phase reactants decreased and her arrythmia disappeared. A month later, the patient took radioactive iodine therapy and she is still euthyroid.
Conclusion: MMI is the first treatment choice in the children with Graves's disease. Although it is more reliable drug than PTU, endocrinologists should be alert for severe side effects of MMI. Cases who were started MMI should be followed closely for adverse effects.

P3-d1-1462 Thyroid 9

Prevalence and etiology of congenital hypothyroidism detected through an Argentine neonatal screening program (1997-2010)

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Introduction: We retrospectively assessed the incidence of CH detected through our neonatal screening program between 1997 and 2010. We describe the diagnostic characteristics of the detected population and verify the impact of the TSH cutoff (CO) change.
Patients and methods: Screening was based on TSH determination on DBS (IFMA) using a 15 mU/L blood CO until 12/2002 (P1) and 10mU/L thereafter (P2). Patients were classified as having transient or permanent CH (athyreotic, ectopic, eutopic, with goiter and unknown etiology). Global and diagnostic related incidences were calculated for the whole studied period with the same CO and P1 and P2 were compared.
Results: Incidences of permanent CH were 1: 3108 (P1) and: 1:2367 (P2). The lower CO detected 22 extra CH, 13 definitive (70 % with eutopic glands.) Only a significant increase ($p < 0.05$) in eutopic CH was found, partially related to the lower CO applied. A statistically significant association with time was seen for total definitive and ectopic cases. ($p < 0.05$).
Conclusion: Our findings revealed some changes in the detected population only partially related to the CO applied, only eutopic dysfunctional disorders being more prevalent in the later years. Total permanent CH and ectopic thyroid disorders showed a trend to higher detection over time but their prevalence has not changed significantly in our screening program.

P3-d1-1463 Thyroid 9

Assessment of the current iodine status via determination of the frequency of transient congenital hypothyroidism in the Central Black Sea Region of Turkey

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Background: Transient congenital hypothyroidism and hyperthyrotropinemia are observed at high frequencies in iodine-deficient areas.
Objective: To determine the proportions of children with transient and permanent thyroid disturbances in a cohort of congenital hypothyroidism (CH); and thereby, to assess indirectly the current iodine status of people living in the Central Black Sea Region of Turkey.
Methods: Medical records of patients diagnosed with CH between January 2003 and December 2012 were retrospectively reviewed. Patients with low or normal FT4 were classified as overt or subclinical CH, respectively. Permanent CH was established if there is
1) absent or ectopic thyroid on imaging or
2) an increase in medication dosage over time or
3) elevated TSH after a 30-day trial off L-thyroxine (L-T4) therapy at ≥ 3 years.
Patients who did not require treatment from baseline or after discontinuation of L-T4 was considered to have transient CH. Undetermined CH included patients who had anatomically normal thyroid glands or were not undergone imaging studies, continued to need L-T4, and were not eligible for trial off because of an age younger than 3 years.
Results: Of the 263 patients, 131 (50%) were found to have transient CH, 50 of whom had transient hyperthyrotropinemia; 79 (30%) were diagnosed with permanent CH; and 53 (20%) remained undetermined. Comparison of selected characteristics in three CH subgroups is shown in Table.
Conclusions: Our study demonstrates that transient thyroid disturbances constitute a great proportion among the etiology of CH, indicating that iodine deficiency remains unresolved problem in our region.

Characteristics	Permanent CH n (%)		Transient CH n (%)		Undetermined CH n (%)		p value
Sex Female-Male	45 (57%)	34 (43%)	54 (41%)	77 (59%)	23 (43%)	30 (57%)	0.07
Birth weight <2500-≥2500 g	9 (12%)	64 (88%)	13 (11%)	105 (89%)	6 (11%)	47 (89%)	0.96
Thyroid function Subclinical- Overt CH	24 (31%)	53 (69%)	50 (39%)	78 (61%)	17 (36%)	30 (64%)	0.52
Treatment No-Yes	0	79 (100%)	21 (16%)	110 (84%)	0	53 (100%)	<0.001
Thyroid imaging Normal-Abnormal	25 (35%)	47 (65%)	103 (99%)	1 (1%)	39 (100%)	0	<0.001
Total	79 (100%)		131 (100%)		53 (100%)		

[Table]

P3-d1-1464 Thyroid 9

Hypothyroidism as the predominant symptom of Albright hereditary osteodystrophy in two children

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Background: AHO is a rare genetic disease due to inactivating mutations of *GNAS1 gene*. The most frequent and typical hormonal features of AHO are the symptoms due to pseudohypoparathyroidism.
Objective and hypotheses: In some AHO patients hypothyroidism is diagnosed firstly and after years they are reevaluated and diagnosed as AHO.
Methods: We present two patients:
Case 1. A girl at the age of 13 years. Since 3 month of life she was treated with L-thyroxine because of increased TSH. During the treatment the normalization of TSH was achieved only when thyroxine concentration exceed upper normal limit. In the patient there were present bone disorders similarly to the features in her mother: shortened metacarpal and metatarsal bones, high-arched palate. At the age of 13 years the patient's height was adequate to parents, normal intellectual development, calcium and phosphates concentration was normal, but PTH was highly increased.
Case 2. A girl at the age of 12 years. Subclinical hypothyroidism was diagnosed at the age of 2 years when she was hospitalized because of constipation and obesity. At the time of diagnosis thyroid gland was of normal size and echogeneity. The treatment with L-Thyroxine was started. At the age of 12 years the girl was admitted to the clinic because of growth inhibition and progressive problems of school performance. Presence of dismorphology of the face and bone malformations. In CNS there were found multifocal calcifications.
Results: In our patients the phenotype and increased PTH with normal Calcium value confirmed AHO.The common mutations in *GNAS1* gene were excluded. Further genetic investigation of *GNAS1* gene was performed.
Conclusions: Dismorphological features present in the patient with hormonal disorders strongly suggest its linkage of genetic disease, which should be insistently searched. In some patients with AHO serum calcium and phosphates concentration can be normal under the hyperstimulation by extremely increased PTH.

P3-d1-1465 Thyroid 9

Acute suppurative thyroiditis in children

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Background: Acute suppurative thyroiditis is a rare but potentially life-threatening disease in children and adolescents, usually occuring as a complication of so-called pyriform sinus fistula. In 90-95% of cases the left lobe of thyroid gland is affected.
A common treatment is a combination of surgical and antibiotic therapy, though good results of less invasive therapeutic approaches are recently reported through nonrandomised studies.
Objective and hypotheses: We present three patients with acute suppurative thyroiditis, without proven pyriform sinus fistula, hospitalized in our institution during a 20-year period. Two of them had a process in the right lobe of the thyroid.
Method: We have retrospectively analyzed medical history, clinical picture, diagnostic procedures and treatment of acute suppurative thyroiditis in three pediatric female patients (ages between 9,5 and 17,7 years) treated at the Department of Pediatrics, Split, Croatia, in the period from 1990. - 2010. year.
Results: Three patients with acute suppurative thyroiditis are described. Two of them had right-sided neck swelling, while the left-sided neck swelling was present in one case, without proven pyriform sinus fistula in all of them. All patients were treated with antibiotics, surgical incision, drainage and thyroid lobectomy. Recurrence of the disease was recorded in one patient, and in two occasions.
Conclusions: We presented three pediatric female patients with a rare but potentially life-threatening suppurative thyroiditis. Variety of clinical symptoms and different ultrasound findings led to additional diagnostic methods in order to confirm the cause of the disease. Two patients had suppurative process in the right lobe of the thyroid gland, unlike most of the cases in which the process is located in the left lobe (90-95%). Pyriform sinus fistula as a cause of suppurative thyroiditis was not proven in all of them.

P3-d1-1466 Thyroid 9

Clinical characteristics of congenital hypothyroidism due to mutations in the thyroid peroxidase gene

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Background: Thyroid peroxidase (TPO) gene mutations are one of the most common causes of thyroid dyshormonogenesis. The occurrence of thyroid carcinoma in patients with congenital hypothyroidism (CH) caused by dyshormonogenesis is very rare, and has only been reported in a few patients harboring mutations in the TPO gene.
Objective and hypotheses: We report three children for two unrelated families with CH due to mutations in the TPO gene. Clinical courses were evaluated over 10 years. All children were diagnosed postnatally by newborn screening. Two siblings had compound heterozygous mutations G182A/G3007A, the remaining patient was a compound heterozygous for C1471T/C1588T.
Methods: These three patients have been following for up to 13 years of age to analysis their clinical, hormonal and imaging evaluation.
Results: Serum concentrations of thyrogloblin (TG) have been changed in parallel with serum levels of thyrotropin (TSH). At a decade of age, enlargement of the thyroid gland was shown in all patients, two of them with multinodular appearance.
Conclusions: Not only serum TSH levels but TG concentrations are important as an index of the control for levothyroxine replacement, and regular neck ultrasound imaging should be recommended because it has been reported the high rate of development of multinodular goiter and the rare occurrence of thyroid cancer in patients with CH due to the TPO mutations.

P3-d1-1467 Thyroid 9

Hyperthyroidism in the absence of thyroid stimulating immunoglobulins in a 5-year-old girl

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Introduction: Hyperthyroidism during childhood is a rare condition, mainly caused by Graves' disease. We describe the case of a 5.5 year old girl with severe hyperthyroidism in the absence of thyroid stimulating immunoglobulins.
Case study: The patient presented with systolic murmur, hyperactivity and loose stools as main symptoms. Furthermore, weight loss and accelerated growth was observed. Thyroid ultrasound revealed an inhomogeneous structure of the gland, by enlargement of both lobes and an increased tracer uptake was noted in scintigraphy. After an initial response to treatment with Methimazole 0.4mg/kg/d, dosages up to 1mg/kg/d were necessary to reach euthyreosis.
Analysis of genomic DNA revealed a heterozygous exchange of a single nucleotide in the TSHR gene. The resulting amino acid substitution located in the third transmembrane domain S505R leads to constitutive receptor activity. Carriers of the specific mutation in 2 families described in literature showed a high relapse rate under conservative therapy. Due to high maintenance dosage and early onset of disease in our patient, total thyroidectomy was performed.
Conclusion: Genetic analysis of TSHR should always be performed in unexplained hyperthyroidism in the absence of stimulating immunoglobulins. Genotype-phenotype correlations can assist in the decision between thyrostatic and surgical treatment.

P3-d1-1468 Thyroid 9

Graves' disease: clinical and therapeutic aspects in 16 paediatric patients

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Background: Graves' disease (GD) management in childhood and adolescence is still controversial.
Objective: To evaluate clinical and therapeutic aspects in pediatric patients with GD.
Methods: Retrospective evaluation of 16 patients with GD followed up for more than 2 years.
Results: The age at diagnosis ranged from 2.0 to 14.9 years (mean: 9.9 years). In the laboratory evaluation we highlight: TSH suppression in all patients, raised free T4 in all patients (and values greater than 5.8 ng/dL in 9 patients) and elevated titers of antiperoxidase and/or antithyroglobulin antibodies in 12 patients. In 5 patients other autoimmune diseases were diagnosed: pemphigus, autoimmune hepatitis and type 1 DM respectively in 1, 1 and 3 patients. All patients received methymazole(MM), and 3 were initially treated with propylthiouracil. In 4 patients the thyroid function is normal 5 months after discontinuation of MM (MM was used respectively for more than 4 years, 2.42 years and 7 months in 2, 1 and 1 patients) and 8 patients have been treated with MM for more than 2 years, with fluctuations in thyroid function. The remaining 4 patients received radioiodine therapy(RIT) at the ages from 10.75 years to 13.92 years (mean: 12.7 years) after have received medical treatment for a mean period of 2.4 years. RIT resulted in hypothyroidism after 2 to 8 months with no side effects. No patient underwent thyroidectomy.
Conclusions: High titles of antithyroid antibodies were common and did not led to remission of GD. Although MM is the first choice of treatment, it is unlikely that pediatric patients with GD will not require other therapies to obtain the complete remission of the disease.

P3-d1-1469 Thyroid 9

Early diagnosed Hashimoto thyroiditis in a context of familial autoimmunity

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Background: Autoimmune hypothyroidism starting in infancy is rare. Rapid diagnosis and treatment are important to avoid psychomotor impairment and growth disorders.
Case study: We report a case of Hashimoto's thyroiditis diagnosed in a 17 month old girl.
Thyroid hormones were measured since this girl gained weight too fast after 12 months without size acceleration, with secondary asthenia and slowing down acquisitions. Free thyroxine (free T4) was low (6.2 pmol/L) and thyroid stimulating hormone (TSH) very high, up to 382.83 mU/L. There was a background of familial autoimmunity: the girl's mother suffered from Crohn's disease, the mother's aunt presented dysthyroidism, and the mother's cousin was affected by type 1 diabetes mellitus.
Neonatal screening for congenital hypothyroidism was normal, and the girl got at diagnosis at 17 month old both normal thyroid ultrasound imaging and thyroid scintigraphy, definitely eliminating congenital hypothyroidism.
Antithyroid peroxidase antibodies were very high (more than 600 kU/L) confirming autoimmune thyroiditis, and diabetes-related autoantibodies were screened positive, confirming global autoimmune background.
Levothyroxine 50 µg per day (3.7 µg/kg/day) was started immediately. Psychomotor development quickly improved: the girl started walking. She initially lost weight and body mass index. Free T4 and TSH normalized under treatment. Actually she is 3 years old, has not developed diabetes mellitus yet.
Conclusions: This girl showed an unusual early presentation of Hashimoto's thyroiditis. We could discuss monogenic glandular syndromes (for example IPEX syndrome or APECED syndrome) in case of associated symptoms.

P3-d1-1470 Thyroid 9

Diagnosis of papillary carcinoma in paediatric patients with ^{99m}Tc scan hyperfunctioning thyroid nodules in a iodine sufficient area

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Background: Thyroid cancer usually has reduced iodine uptake and normal thyroid function. Rarely cancer is reported in hyperfunctioning nodules. Higher incidence is reported in iodine deficient areas soon after introduction of iodinization. Fine needle aspiration biopsy (FNAB) of hot nodules is not routinely performed.
Objective and hypotheses: We report three adolescents from an iodine sufficient area with hyperfunctioning thyroid nodules which upon surgery, revealed a papillary carcinoma.
Results: Case 1(14yrs) was referred due to a firm nodule, ultrasound (US) showed an heterogeneous irregular cystic-solid mass of 19x14x13mm, scintigraphy (SC) revealed an hyperfunctioning nodule. Due to US findings, family history of thyroid cancer and unsatisfactory FNAB, thyroidectomy was performed which revealed a carcinoma. Case 2(13yrs) was referred due to a firm nodule, US showed a cystic-solid nodule of 6x3.5x4cm, hyperfunctioning at SC with almost total inhibition of contralateral lobe. FNAB was benign, thyroidectomy allowed diagnosis of carcinoma.Case 3(15yrs) referred due to a firm nodule, clinic finding suggesting hyperthyroidism was observed. Laboratory: TSH < 0.01 mUI/ml (0.3 -5) T4l: 2.24 (0.8-2.1) T4: 12.2 ug/dl (4.5-13) T3: 2.3 ng/dl (0.8-2.0), TSH receptor antibody (TRAb) 2.8 % (0- 1.75) allowing diagnosis of Graves disease. US showed a heterogeneous irregular solid nodule of 23x13x21mm with micro-calcifications. It was hyperfunctioning with normal uptake in the rest of the gland. Nodulectomy lead to diagnosis of papillary carcinoma within the nodule.
Conclusions: Thyroid glands with hot nodules need to be carefully evaluated because malignance can be present even in the presence of Graves disease, an entity very rarely associated with malignancy in pediatric age. Further studies will determinate which is the best strategy for accurate diagnosis and treatment of hot nodules in pediatrics.

P3-d1-1471 Thyroid 9

Thyroid function of critically-ill infants in the intensive care setting

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Background: Abnormal thyroid hormone levels have been reported in a variety of patients with diseases other than thyroid gland pathology. Previous studies reported on the spectrum of thyroid function abnormalities in critically ill neonates. Thyroid function abnormalities are among the factors associated with poor neurodevelopmental outcome, especially in preterm and critically-ill infants.
Objective and hypotheses: To describe the thyroid hormone profile in critically ill newborns, and determined whether thyroid function abnormalities are more common in sick preterm or term infants.
Methods: A cross sectional study of infants who admitted to the neonatal intensive care unit (NICU) of the H.Adam Malik Hospital, Medan, between August 2012 until February 2013. We enrolled all critically ill infants with infection, respiratory, cardiology, digestive, and neurology problems. Serum T3, T4, and TSH levels were measured during hospitalized. The data was analyzed by Mann Whitney test.
Results: There are 27 critically ill infants from the neonatal intensive care unit (NICU) were entered to our study. Of all the included neonates, 14 were premature and 13 were term infants. The laboratory parameters of thyroid function include low or normal T3, normal or low levels of T4, and normal or

high of TSH levels, and we found there was no significant difference of TSH, T3, and T4 levels between sick preterm and term infants (p>0,05).
Conclusions: There was no significant difference of thyroid function between critically ill premature and term infants in our hospital and there was no baby got thyroid hormone. Further follow up need to evaluate the thyroid function in critically ill infants that correlate with clinical outcome.

P3-d2-1472 Thyroid 10

An evaluation of the effects of carbamazepine on thyroid function tests in childhood epilepsy

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Objective and hypotheses: To investigate the effects of carbamazepine (CBZ) treatment on thyroid function tests in children
Methods: The CBZ group consisted of 58 children monitored for epilepsy and a control group consisting of 54 healthy children. Age at onset, duration of drug use, drug dosage and laboratory parameters including free triiodothyronine (FT3), free thyroxin (FT4) and thyrotropin (TSH) were recorded. These data were then compared with those of the control group.
Results: CBZ group values were FT3 3.86 ± 0.43 pg / mL, FT4 1.15 ± 0.18 mg/dL and TSH 2.58 ± 1.33 ml U/L, respectively. Control group values were FT3 4.13 ± 0.59 pg/mL, FT4 1.34 ± 0.13 mg/dL and TSH 2.06 ± 0.89 ml U/L. The rates of subclinical hypothyroidism were not statistically significantly different between the two groups (P = 0.196).
Conclusions: CBZ reduces thyroid hormone concentrations, but rarely causes hypothyroidism.

P3-d2-1473 Thyroid 10

Follow-up of congenital hypothyroidism: from screening to precocious treatment

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Background: We describe the experience of the Paediatric Clinic in Palermo about children with congenital hypothyroidism (CH).
Methods: 132 positive screening newborns, confirmed at the second screening when recalled for the first pathological relieve, were diagnosed at the "Screening Center for Congenital Hypothyroidism" operating at the "Children Hospital" of Palermo; among these, 95 were followed in the period 2010-2012, by the Paediatric Clinic of Palermo. The blood spot relieves were confirmed by serum dosage of TSH, fT_3 and fT_4 hormones, thyroid scan and/or scintigraphy.
Results: All the patients were born at term (gestational age: 38,9 ± 1,9 w), with a weight: 3028 ± 633 gr; length: 49,6 ± 2,4 cm. TSH value at the first screening was 22,56 ± 45,40; at the recall was 43,65 ± 85,36.
10 patients were sons of mothers with thyroid diseases, already treated with replacement hormonal therapy or diagnosed at the time of the screening.
Gestational age was 38±1 weeks (range: 33-42); birth weight: 3212±459,7 gr. They showed TSH levels 27,2 ± 53,33 at the first screening; 43,94 ± 86,21 at the second. At the first serum detection TSH levels were 83,8 ± 163,6.
The aetiology of thyroid failure was 5% ectopic gland, 5% agenesis, 7% hypoplasia, 82% thyroid *in situ.*
Conclusions: The adequate collaboration between the Screening Center and the Paediatric Clinic guaranteed the replacement with hormonal therapy within 15-21 days of life in 90% of the patients.

P3-d2-1474 Thyroid 10

One case report of thyrotoxic myopathy and review

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Background: Diagnosis of this patient was thyrotoxic myopathy. thyrotoxic myopathy is very rare in pediatrics patients. It is easily neglected because of the insufficiecy cognition or its positive process by paediatrcicians.
Objective and hypotheses: Approach the clinical characteristic, diagnosis and treatmnet of thyrotoxic myopathy order to improve cognition and treatment of this disease.
Methods: Discribe one case of thyrotoxic myopathy in Beijing Children Hospital, analyze clinical manifestation, laboratory examination, diagnosis and therapeutic method of this case. Meanwhile review literatures to gain relevant knowledge and progression of thyrotoxic myopathy.
Results: Clinical manifestations of this patient were woking unsteadly, masule weakness, diarrhea and weight loss obviously simultaneously. (Thyroid functiong test : TT_3 208.2ng/dl TT_4 13.83μg/dl TSH 0.01μ IU/ml FT_3 11.04pmol/L FT_4 35.28 pmol/L), MRI of Lumbosacral vertebrae was normal. Electromyogram was no abnormality seen. Biopsy of quadriceps femoris muscle was muscle fibers swelling and degeneration. Immunofluorescence was negative (IgA IgG IgM C_3 C_4 C_{1q} f). Significant effect with administration Thyrozo(1mg/kg) and prednisone(1mg/dl) in this patient.
Conclusions: Diagnosis of this patient was thyrotoxic myopathy. thyrotoxic myopathy is very rare in pediatrics patients. It is easily neglected because of the insufficiecy cognition or its positive process by paediatrcicians. This paper clues on that this disease should be noticed to discovery and treatment, with taking appropriate therapy of this disease to pediatricians.

P3-d2-1475 Thyroid 10

Congenital hypothyroidism in Palermo: epidemiological data of the screening center in the years 2010-2012

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Background: Congenital hypothyroidism (CH) is the most frequent endocrine disease in children caused in most cases by alterations in the embryogenesis of the thyroid gland; hormone deficiency has elective influences on the nervous system development and on growth. Good timing and adequate replacement with levothyroxine prevent damages.
Methods: We report the results of the "Screening Center for Congenital Hypothyroidism", operating at the "Children Hospital" of Palermo, in the period 2010-2012.
Results: We identified 2024 newborns with a first positive screening for CH (group A, TSH value: 8,4 ± 9,25) not confirmed at the second recall; 132 newborns also with the second pathological screening (group B, TSH value at the first screening: 22,56 ± 45,4; TSH at the second screening: 43,65 ± 85,36). No significant difference was relieved between the two groups for time at the screening, gestational age, neonatal weight.
TSH values were significantly lower in group A than in group B; in group B the second screening TSH was significantly higher than the first one, confirming the diagnosis.
All the patients belonging to group B were confirmed as hypothyroid ones by detecting the serum value of TSH, fT_3 and fT_4 hormones, thyroid scan and/or scintigraphy.
In group B 62 newborns (47%) at the first screening had TSH < 10; 26 (20%) had TSH < 7. Furthermore 42% were recalled because the point of cut-off of TSH, considered pathological, is considered today > 7 mU/l. However the geographic origin of the pathological patients was mainly from districts with iodine deficiency.
Conclusions: We highligth the fundamental role played by setting the TSH cut-off < 7 for neonatal screening.

P3-d2-1476 Thyroid 10

Hyperthyroidism in children and adolescents with different clinical conditions

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Background: Hyperthyroidism is considered to be rare in children.
Objective and hypotheses: To study epidemiological and etiological features and clinical course of hyperthyroidism in a heterogeneous group of paediatric patients.
Methods: Retrospective analyses of the clinical records of patients treated by paediatric endocrinologists in our institution for hyperthyroidism.
Results: The group included 40 children and adolescents (34 F, 6 M) with hyperthyroidism of different origin. There were 32 patients with Graves' disease (GD) and 8 with different genetic syndromes: 4 with Down syndrome, 2 McCune-Albright syndrome patients, one child with Treacher-Collins syndrome and one with selective pituitary resistance to the thyroid hormone. The patients' average age at hyperthyroidism diagnosis was 10,4±3,5 (range 2-15,8) years, their average age at the time of the study was 14,4±4,0 (range 4,3 - 20,6) years. The time of follow-up was 48,7±32,9 months. Ten patients (25%) had the thyroid problems in the first degree relatives, mostly female. In the whole group, 12/40 (30%) of the patients had other autoimmune diseases: AIO, juvenile rheumatoid arthritis, asthma, alopecia. The differences in clinical manifestation according to the age and co-existing diseases, in clinical course and approaches to and problems of treatment in children will be demonstrated. We observed rather high rate of relapses in GD, comparative to the other studies. Four adolescents were treated surgically. The reasons for an alternative treatment were very large goiter; severe thyrotoxicosis, resistant to treatment with anti-thyroid drugs; thyrotoxicosis relapses after two courses of conservative treatment, also poor patient compliance due to mental retardation.
Conclusions: Our study demonstrated that hyperthyroidism in children may be attributed to different clinical conditions which can influence the approaches to such patients and require endocrinologist's experience.

P3-d2-1477 Thyroid 10

Interobserver agreement in detecting goitre by palpation in a school population

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Background and objective: To estimate the agreement between observers on the detection of goitre by physical exploration in a school population.
Methods: We performed a cross-sectional study to detect goitre in a representative sample of 1134 schoolchildren aged 6 to 12 years from 20 schools in the health area of La Mancha Centro (Spain). The examination was performed blinded by two observers. Five grades in thyroid size were established (0, Ia, Ib, II and III). Above grade Ia was considered as goitre. The agreement was assessed in relation to variables such as age, sex, body mass index, height, and day of examination. The weighted kappa was used to measure the agreement.
Results: In the 1097 schoolchildren with a dual examination, 96 (8.8%) cases of goitre were detected by observer 1, and 102 (9.3%) cases by observer 2, (P=.58). The degree of interobserver agreement in the identification and grading of goitre was moderate (kappa 0.55, 95%CI: 0.46 to 0.64) for the first, and substantial (weighted kappa 0.61; 95%CI: 0.51 to 0.71) for the second. The degree of agreement was somewhat higher in girls, older schoolchildren, increased weight, height, and body mass index. The interobserver agreement was relatively stable throughout the study.
Conclusions: The interobserver agreement in detecting goitre by palpation in our study is moderate, but is lower in younger children and stable for the duration of study.

P3-d2-1478 Thyroid 10

Abstract has been withdrawn

P3-d2-1479 Thyroid 10

Gender- and age-related characteristics of the course of autoimmune thyroiditis in children

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Background: Autoimmune thyroiditis(AIT) is a common etiology of acquired thyroid dysfunction in pediatrics, optimal quantities of thyroid hormone are critical to neurodevelopment and growth.
Objective and hypotheses: To study characteristics of thyroid status of children with AIT at the manifestation of the disease and during hormone replacement therapy.
Methods: A retrospective analysis of 95 (girls/boys =80/15) patient cards of children with AIT was conducted. Depending of the Tanner stages of sexual development the patients were divided into groups of girls: pre-puberty G1 (Tanner I) 31,25%, early puberty G2 (Tanner II-III) 43,75%, late puberty G3 (Tanner IV-V) 25%, and boys: pre-puberty B1 (Tanner I) 40%, puberty B2-3 (Tanner II-V) 60%. Data processing was carried out using Exel 2010. The differences were judged to be statistically significant at $p< 0,05$.
Results: 36,84% of children had burdened family history of thyroid diseases. Complaints with manifestation were in G1 - in 40%, in G2-3 - 32,7%; in B1 - 33,3%, in B2-3 - 44,4%.
Among the girls hypertrophic form of AIT was found in 87,5%, normotrofic - 11,25%, atrophic - 1,25%. Among the boys hyper- and normotrofic forms were in 86,7% and 13,3%. At manifestation among the girls euthyroidism was observed in 21,25%, subclinical hypothyroidism - 61,25%, overt hypothyroidism - 15%, hasitoksikosis - 2,5%; among the boys: euthyroidism -40%, subclinical hypothyroidism - 33,3%, overt hypothyroidism - 26,7%. Treatment with levothyroxine was received in G1 -92%, the dose 1,20±0,48 mg/kg, in B1 - 100%, the dose 1,20±0,46 mg/kg, in B2-3 - 66,67% the dose 1,07±0,16 mg/kg, the dose for G2-3 was 0,82±0,37 mg/kg ($p=0,013$).
Conclusions: Hypertrophic forms of AIT dominate regardless of age and gender. Latent or overt hypothyroidism is typical for manifestation of AIT in children. It's required smaller doses of levothyroxine for substitution therapy in girls with the development of puberty, compared with their peers.

P3-d2-1480 Thyroid 10

Prevalence of sensorineural hearing loss in patients with congenital hypothyroidism

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Background: Congenital hypothyroidism is mainly diagnosed through neonatal screening program. Normal physical and mental development can be maintained with pertinent replacement therapy. One of the associated abnormalities in these patients is the sensorineural hearing defect, which has a prevalence of about 20% according to relevant references.
Objective and hypotheses: To obtain the prevalence of sensorineural hearing loss in children with congenital hypothyroidism identified in the screening program in Qazvin, Iran.
Methods: All patients afflicted with congenital hypothyroidism identified in the screening program (in Qazvin, Iran) were enrolled in this study. They were both under observed and hormonal replacement therapy by referral Endocrine Diseases Clinic and auditory brainstem responses test (ABR) was performed for all subjects.
Results: Of 169 patients with congenital hypothyroidism, 42.3% were female. The prevalence of sensorineural hearing loss was 5.3% (6 male, 2 female). Statistical analysis did not reveal any significant difference between the prevalence of sensorineural hearing loss with other variables of the study.

Conclusions: A remarkable difference was observed between the results of our study with those stated in the references. Normal sensorineural hearing can be maintained with pertinent replacement therapy.

P3-d2-1481 Thyroid 10

A comparison of subclinical hypothyroidism and 25-hydroxyvitamin D levels in children using valproic acid

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Objective and hypotheses: The purpose of this study was to examine the subclinical hypothyroid-inducing effect of valproic acid (VPA), a frequently used anti-epileptic, and its effects on bone mineral metabolism.
Methods: Free thyroxine, thyroid stimulating hormone, 25 hydroxy vitamin D (25OHD) and parathormone levels in serum specimens from epilepsy patients using VPA were compared with specimens collected from a control group. Subjects with subclinical hypothyroidism and 250HD deficiency were identified.
Results: The presence of subclinical hypothyroidism in patients using VPA was statistically significant compared to the control group. There was no significant difference compared to the control group in terms of serum 25OHD and parathormone levels
Conclusions: It does not seem possible to regard subclinical hypothyroid identified in the early period as an early marker in bone mineral disorders that may develop in the late stage in association with VPA.

P3-d2-1482 Thyroid 10

Electrocardiographic changes of corrected QT prolongation in hyperthyroidism

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Background: There have been few reports about the electrocardiographic (EKG) changes of corrected QT (QTc) prolongation in hyperthyroidism.
Objective and hypotheses: Therefore, we studied about EKG QTc changes in hyperthyroidism.
Methods: We investigated, retrospectively, the clinical records of 91 hyperthyroid patients less than 30 years old which were possible to show their EKGs from Aug, 2003 to Aug, 2011 in Hallym University Medical Center. We used the criterias in which the absolute QTc prolongation was 450 ms in men, $\geq$ 460 ms in women and the borderline QTc prolongation was 430-449 ms in men, 440-459 ms in women, excluding left ventricular hypertrophy and right/left bundle branch blocks.
Results: Among the total 91 patients, 21 (23%) showed QTc prologation in which 13 (14.3%) were in absolute QTc prolongation and 8 (8.8%) were in borderline QTc prolongation. And among the 21 patients of QTc prologation, 9 (42.9%) were men and 12 (57.1%) were women, and their mean age were 21.7 years old. In the two men associated with hypokalemia (thyrotoxic hypokalemic paralysis), their absolute QTc prologation were even over 550 ms (up to 619 ms). And another three patients (1 men, 2 women) also showed severe QTc prologation over 500 ms (up to 569 ms) without any associated abnormalities.
Conclusions: We report that QTc prologation would be sometimes present in severe hyperthyroidism. Because QTc prologation might be proarrhythmic, we think that the EKG changes should be carefully followed up in severe hyperthyroidism and also it should be realized that the QTc prologation could be a maker for the severity of hyperthyroidism.

Late Breaking **Abstracts**

LB1-1489 Adrenals, Bone and Endocrine Oncology

A patient with primary adrenal insufficiency presenting with persistant hyponatremia

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Background: OPS typeIIis diagnosed in cases with chronic lymphocytic thyroiditis and/or immune diabetes mellitus with adrenocortical insufficiency which is the main result of autoimmune adrenalitis presenting in about 50% of the cases. Here, a patient who was already being followed for autoimmune thyroiditis for last one year and diagnosed with primary adrenal insufficiency on evaluation for current hyponatremia will be discussed.
Case: The male patient aged 8 years and 10 months was presented to the emergency service with fever and vomiting and hospitilised for hyponatremia and dehydration. Despite intensive treatment, there was no significant improvement in the patient's hyponatremia and clinical status. So basal cortisol level was measured, which was1.05 µg/dL (6.7-22.6) with ACTH level of1500 pg/mL. So the patient was diagnosed as primary adrenal insufficiency. The patient was taking L-thyroxin for thyroiditis. Physical examination: height:129.7cm (50-75p), weight: 22.5 kg (10-25 p). He was in poor clinical status with aphthous stomatitis. Generalized pigmentation with areas of more marked pigmentation extending from the mandibula to the neck was present. He was prepubertal with bilateral testicles at scrotum, volume was 2 ml. Laboratuary examination: blood glucose: 73 mg/dl, Na: 121 mmol/l, K: 5,47mmol/l, Cl: 97 mmol/l. Basal cortisol was 1,05µg/dL (6,7-22,6) ACTH: 1500pg/mL, renin 11,6µIU/ml, aldosterone 2,80 pg/ml. Celiac antibodies: negative, anti-insulin antibody: (-), anti-GAD: (-). The patient was started immediately 100 mg/m2/day hydrocortisone and fludrocortisone. Patient's overall condition improved dramatically with treatment. Na was measured as135 mmol/l on the second day of the treatment. He was discharged with hydrocortisone dose of 20mg/m2/day. Adrenal MRI: Normal. 21-OHantibody: positive.
Conclusions: In patients with refractory hyponatremia and mild hyperkalemia, 'adrenal insufficiency' should be considered regardless of the patient's age and the patient should be investigated accordingly.

LB1-1490 Adrenals, Bone and Endocrine Oncology

Identification and characterisation of a novel mutation (IVS5-2A>G) in the CYP21A2 gene in a patient with classical virilizing congenital adrenal hyperplasia (CAH) with two rares mutation

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Background: In classical (C) CAH patients due to 21OHD more than 90% of CYP21A2 mutant alelles present gene deletions or pseudogen derived mutations. Patients carryng none of these mutations are unlikely to be affected.
Objective and hypotheses: We report a CCAH patient who presented a rare and a novel CYP21A2 mutation.
Methods: Clinical evaluation and hormonal measurements were performed. DNA samples were analyzed for the CYP21A2 pseudogene-derived mutations, southern-blot and direct sequencing. Functional consequence of the novel mutation was assesed by RT-PCRafter transfection of splicing reporter-wild type and mutated minigenes in HEK-293 ,HeLa and Y-1 cell lines.
Results: A 31 year- old woman was referred to reevaluate the diagnosis of CAH. At the age of 6 months she presented with clitoromegaly advanced bone age and pubic hair. She was dignosed as 21OHD and treated with prednisone until the age of 8 yr. She never had surgical correction of her genitalia. Between 12 to 18 yr, she was treated again and presented menarche. Physical examination disclosed: Height: 159 cm, _0.1SDS, well developed breasts, moderately hirsutism and no sexual ambiguity except for a mild clitoromegaly (Prader I) Hormonal follicular phase levels were: 17OHP Basal: 300 ng/ml, stimulated: 1.050 ng/ml, Androstenedione: 16ng/ml,T: 21 ng/ml. None of the pseudogen derived mutations werw found. Direct sequencing revealed that the patient was compound heterozygous of the rare p.R453Q mutation and a novel IVS5-2A>G one. Functional assays disclosed that IVS52AG mutation abolished the use of the canonical splice site. Instead a crypting splicing acceptor site within exon 6 creates an mRNA with 16nt deletion causing the appearance of a premature stop codon.
Conclusions: When clinical and biochemical findings strongly suggest 21OHD, sequencing the entire gene is needed to further exclude the diagnosis. Functional studies should contribute for a better understanding of phenotype -genotype correlations.

LB1-1491 Adrenals, Bone and Endocrine Oncology

A longitudinal study of bone biochemical markers in postmenarchal adolescent girls: relationship with gynecological age, body mass index, race/ethnicity, and serum estradiol levels

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Background: While multiple studies have explored bone mineral density accrual during the early postmenarchal years, less is known about bone biochemical markers (BBMs) during this time period.

Objective and hypotheses: To investigate relationships between BBMs and gynecologic age (GA), body mass index (BMI), race/ethnicity, and serum estradiol in postmenarchal female adolescents
Methods: A multi-center, prospective, longitudinal, study that assessed BBMs changes in 120 postmenarchal healthy girls aged 11-18 years. Markers of bone formation (serum bone specific alkaline phosphatase, BSAP, serum osteocalcin, OC) and bone resorption (urinary N-telopeptide, uNTX) were measured by enzyme-immunoassay, and serum estradiol was measured by chemiluminescence-immunoassay, at baseline, 24, 60, 84, 120, 144, 180, 204, and 240 weeks. Generalized estimating equations were used to examine BBMs changes throughout this 240 week-study.
Results: Participants had a mean (±SD) age of 14.2±1.6 years, mean (±SD) GA of 33.5±22.0 months post menarche, and mean (±SD) BMI of 23.4±4.8 kg/m^2 at baseline. Ethnic/racial distribution was 54 African-American, 48 Caucasian, and 18 Hispanic. All participants denied cigarette smoking and alcohol consumption. Estradiol levels did not significantly vary by GA, BMI, or race/ethnicity. Within girls, as estradiol fluctuated throughout the study, estradiol levels were inversely related to uNTX levels (P=0.0013). There was no significant relationship between estradiol and BSAP and between estradiol and OC. Greater GA (p=0.0002) and BMI (p=0.0113) were each inversely and additively related with OC. There was no significant relationship between BBMs and race/ethnicity.
Conclusions: Estradiol levels are inversely related to the bone resorption marker uNTX during postmenarchal years in adolescent girls. Greater GA and BMI are inversely associated with the bone formation marker OC throughout this time period.

LB1-1492 Adrenals, Bone and Endocrine Oncology

A novel CLND16 mutation in a large family with familial hypomagnesaemia with hypercalciuria and nephrocalcinosis

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Introduction: Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis is a rare tubulopathy leading to renal calcification and progressive renal failure.
Case: We report a consanguineous Arab family (of Qatari origin) with 7 affected siblings with variable phenotypes including hypomagnesaemia, hypercalciuria, nephrocalcinosis and renal stones. Presenting features included haematuria and recurrent urinary tract infections. As the biochemical and clinical phenotypes of this family resembled familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, we performed genetic investigation in order to provide a precise molecular diagnosis. We screened all coding regions of the *CLND16* gene and identified a novel mutation (c.G647A, p.R216H) which was found homozygously in the six severely affected cases, who manifested significant nephrocalcinosis, often nephrolithiasis and sometimes reduced GFR. Parents were both heterozygous for the mutation and, together with children carrying the mutation in its heterozygous state, exhibited mild or no biochemical phenotypes.
Conclusion: Mutations in *CLND16* underlie familial hypomagnesaemia with hypercalciuria and nephrocalcinosis but remain a rare cause of nephrocalcinosis and nephrolithiasis. Management includes reduction of hypercalciuria with thiazide diuretics, correction of serum magnesium and close monitoring of renal function given the significant risk of end stage renal failure with this inherited form of nephrocalcinosis.

LB1-1493 Adrenals, Bone and Endocrine Oncology

WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta identify a key WNT ligand regulating bone mass

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Background: The role of the WNT pathway in skeletal maintenance has been extensively studied since the identification of mutations in key signaling WNT mediators in high and low bone mass phenotypes. However, the identity of the key WNT ligand has remained unknown.
Objective and hypotheses: To identify genes with a major effect on the skeleton by studying individuals and families with early-onset osteoporosis or osteogenesis imperfecta (OI).
Methods: We recruited a Finnish family with severe early-onset and dominantly inherited osteoporosis, characterized by low BMD and vertebral fractures, in 10 individuals. We also ascertained a Laotian Hmong family with two severely affected daughters suffering from recessive OI.
Results: A genome-wide microsatellite scan, fine-mapping and targeted next-generation sequencing of the linkage region identified a single novel variant in *WNT1* (p.C218G) segregating with the phenotype. In the family with OI we performed whole-exome sequencing and identified a homozygous nonsense mutation in *WNT1* (p.Ser295*) in both affected children. The WNT1^{C218G} and WNT1^{S295*} showed significantly reduced capacity to induce canonical WNT signaling in a TOPFLASH reporter assay. They also had impaired capacity to induce the WNT target gene expression and osteoblast differentiation in vitro. Expression profiling by RT-PCR showed *Wnt1* expression in mouse brain, femur and spleen but not in calvarial osteoblasts, osteoclasts or human mesenchymal stromal cells. *Wnt1* was clearly expressed in bone marrow, especially in B cell lineage and hematopoietic progenitors. Using a Wnt1-Cre crossed with a reporter mice Wnt1 expression was also detected in a subset of osteocytes.
Conclusions: These findings indicate that loss-of-function heterozygous or bi-allelic mutations in *WNT1* result in early-onset osteoporosis or OI and identify WNT1 as a key WNT ligand in the regulation of bone mass.

LB1-1494 Adrenals, Bone and Endocrine Oncology

Metabolic profile after treatment in child and adolescent in patients with acute lymphoblastic leukaemia (ALL)

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Background: Acute Lymphoblastic Leukemia (ALL) is the most common form of cancer in children. However, survivors are at risk for long-term complications of treatment like obesity and metabolic disorders.
Objective and hypotheses: Describe the rate of obesity and metabolic profile after treatment in child and adolescent patients with ALL and compare three treatment groups (A = Radiotherapy without bone marrow transplantation

(BMT), B = Radiotherapy with BMT and C= Without Radiotherapy).
Methods: Cohort study of 41 disease-free survivors ALL patients were aged ≤ 18 years old at the moment of ALL diagnosis and had, at least, 2 years without cancer treatment. The patients underwent clinical examination and analysis evaluation of: insulin, fasting glycemia and lipid profile.
Results: 41 patients 22 male (M) and 19 female (F) were evaluated, respectively aged from 8,7 to 28,6 years old (mean 16,5±5,2) and 7,2 to 27,8 years old (mean 17,6 ±6,8). 13(7F 6M),16(5F 11M) and 12 (7F 5M) were in A, B and C treatment groups, respectively. There were 18 patients with hormone deficiency and all of them were undergoing hormone replacement therapy. Obesity was present in 4(9,8%) patients, 1 male and 3 female. The mean homeostatic model assessment insulin resistance (HOMA-IR) value was similar (p=0,79), between gender 3,5±2,2(F) and 2,9±2,3(M), and different (p=0,014) between treatment groups 2,6±2,0; 4,4±2,5 and 2,2±1,2 in A, B and C groups, respectively. Lipid disorders occurred in 15(36,6%) subjects and it was not associated with treatment or gender group (p=0,35). Fifty percent of the patients who had hormonal deficiency presented lipid disorders.
Conclusions: The number of obesity patients was low. The HOMA-IR was higher in patients who underwent radiotherapy with bone marrow transplantation. The lipid disorders were similar between treatment groups and were observed in half of patients with hormone deficiency.

LB1-1495 Adrenals, Bone and Endocrine Oncology

Ovarian reserve (OR) in young woman diagnosed with lymphoblastic leukaemia (ALL) during childhood and adolescence

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Background: Advances in treatment have improved survival of patients with leukemia but could lead to infertility and decrease in OR.
Objective: Assess ovarian function in young women treated with chemotherapy for ALL in infancy.
Methods: We evaluated women treated for ALL during childhood and adolescence (ALLW, N=33, 15-35 yr) according to a Chilean standardized treatment protocol (age: 21.3±4.4 yr) that had completed treatment at least 5 years earlier. Physical exam, pelvic ultrasound and FSH, estradiol and Antimüllerian hormone (AMH) were determined and compared with a group of healthy women (C, N=47 age 27.5±73 yr).
Results: ALL were diagnosed at 6.2±4.2 yr with intermediate and standard risk in 57 and 37% respectively. Patient were diagnosed at 0-7 yrs in 24.2% and between 9 -15 yrs in 75.8%. Age of menarche (AM) was 12.5±1.4 yr. AM >15y(15,16,17y) in 9%, amenorrhea was observed in18.7% and irregular menses in 18.1%, live births in 21.2%. FSH, ovarian volume and follicle number were similar in ALLW and C, estradiol was significantly lower in ALLW vs C (24±24 vs 68±32 p< 0.01). AMH was higher in ALLW vs C (5.5±2.7 vs 2.2±1.5ng/ml p< 0.01). However, two patients had FSH≥10. As expected AMH positively correlated with OV and FN.
Conclusions: With standard doses of chemotherapy, OR often is retained. Young patients treated with chemotherapy for ALL in infancy appear do not have significant impairment of OR during the second and third decade of life.

LB2-1496 Fat Metabolism, Obesity

Analysis of the influence of CLOCK 3111 T/C SNP on the presence of obesity and duration of sleep in children

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Background: Childhood obesity is a health public problem worldwide. The inefficiency of traditional approaches to explain this epidemic has lead to new attempts to comprehend environmental and genetic influences, such as those involved in the control of circadian rhythms.
In adults, a polymorphism located in the CLOCK gene, named 3111 T/C (rs1801260), has been associated to sleep duration, ghrelin levels, feeding pattern and weight.
Although short sleep duration has been related to obesity in children, few studies have been directed to identify potential molecular mechanisms of this association.
Objectives: To assess the relationship between CLOCK 3111 T/C SNP and the presence of obesity, as well as sleep duration, in children.
Methods: Cross-sectional study involving children aged 6 to 13 years. A questionnaire about sleep hours, physical activity and socioeconomic data was given to parents. Weight, height, waist and hip circumferences were assessed twice and converted to z-scores for age and sex. Genotyping was performed by *Taqman* methodology. Hardy Weinberg equilibrium was verified and appropriate statistic tests were performed.
Results: A total of 370 children were evaluated (45%male, 55%female, mean age:8,5±1,5 ys). Only 27% of them performed regular physical activities.The prevalence of excess of weight was 18%.The sleep duration was, on average, 9,7hs. It was inversely related to age (p< 0,001).
Genotype distributions were: 4% CC, 31% CT and 65% TT. There was a tendency to higher prevalence of excess of weight in children who slept less than 9h(23%), when compared to children who slept more than 10h(16%; p=0,06). Genotype was not significantly associated to any of the assessed endpoints.
Conclusions: The CLOCK 3111 T/C SNP is not significantly associated to excess of weight or sleep duration in children from this locality. Further studies on molecular regulators of circadian rhythms, with enhanced statistical power, must be conducted in children.

LB2-1497 Fat Metabolism, Obesity

Association study of polymorphisms in FTO with childhood overweight and obesity

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Background: The fat mass and obesity associated gene (FTO) expressions have been implicated in the development of obesity.
Objective and hypotheses: To investigate whether SNP polymorphisms of FTO might be associated additionally with metabolic traits in Chinese children.
Methods: Targeted genotyping of five common single nucleotide polymorphisms (SNPs: rs1421085, rs17817449, rs8050136, rs3751812 and rs9939609) was performed using an automated platform MassARRAY for 405 obese or overweight and 194 normal children.
Results: When all obese or overweight cases were compared with all normal cases, significant differences were found in the allele frequency and in the genotype distribution. Compared with the wide-type genotype, minor allele carriers of the five SNPs were associated with increased risks of childhood obesity or overweight (rs1421085, OR = 1.980; rs17817449, OR = 2.011; rs8050136, OR = 1.925; rs3751812, OR = 1.911; rs9939609, OR = 1.930). After adjustment of age, sex and BMI-z score, all of the five SNPs showed a trend towards higher SBP. In addition, rs3751812 and rs8050136 showed significant association with LDL-C and HOMA-IR levels. Strong evidence of total association was found for BMI in relation to haplotype TTCGT and haplotype CGATA (after 10000 permutations, *P*=0.015 and 0.011, respectively)

Conclusions: In conclusion, genetic variation in the FTO locus contributed to the etiology of obesity, hypertension, insulin resistance, and increased plasma LDL levels.

LB2-1498 Fat Metabolism, Obesity

Circulating lipoprotein-associated phospholipase a2 levels are elevated in obese children

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Background: Obesity and cardiovascular disease are often co-morbid, but the pathophysiologic mechanisms that link the two are not fully understood. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is involved in the modification of lipids within atheromas and was recently found to be predictive of thromboembolic episodes in adults.
Objective and hypotheses: To study Lp-PLA2, a nontraditional risk factor of cardiovascular disease (CVD), in obese children.
Methods: 67 lean (39 boys- 28 girls, mean BMI z-score: -0.23 ±0.78) and 66 obese (32 boys-34 girls, mean BMI z-score: 4.39 ±1.18) age-matched (p=0.08) children, aged 6-12 years, were studied. All children had a physical examination and morning blood drawn after 12h of fasting. Glucose, insulin, lipid profile and Lp-PLA2 were determined. Plasma concentrations of Lp-PLA2 were determined by an enzyme-linked immunosorbent assay (ELISA) kit (PLAC Test). BMI z-score was calculated and children were categorized as obese according to the Cole criteria.
Results: Plasma Lp-PLA2 levels were significantly higher in obese children (322.5 ± 77.8 ng/ml) than those of the normal weight group (278.0 ± 64.4ng/ml), (p< 0.00001). Lp-PLA2 concentrations were significantly correlated with the BMI z-score (p=0.006).
Conclusions: We found significantly higher Lp-PLA2 levels in obese children than lean controls. Interestingly, they all had levels >200 ng/ml, which are thought to correlate with atherosclerosis and a high thromboembolic risk in adults. The positive correlation of Lp-PLA2 with BMI reveals an effect of obesity on this marker, which suggests vascular involvement caused by the increase of weight, even at a very young age. More prospective studies should be done in order to evaluate whether Lp-PLA2 could be added to the panel of tests used to identify young individuals at high CVD risk.

LB2-1499 Fat Metabolism, Obesity

Internalizing and externalizing symptoms in obese children: associations with daily salivary cortisol concentrations

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Background: Obesity commonly co-exists with anxiety and depression (internalizing disorders) in youth, whereas recent data show co-existence of obesity with attention deficit-hyperactivity disorder and rule breaking behavior (externalizing disorders/symptoms). Disturbed cortisol concentrations have been reported in chronically stressed individuals with stress-related disorders.
Objectives and hypotheses: We investigated the prevalence of internalizing (IS) and externalizing (ES) symptoms, reported by both parents and children, in obese children compared to normal-weight ones. In addition, we examined the role of cortisol as a potential mediator between stress-related symptoms and obesity.
Population and methods: 110 (50% females) obese children (mean BMI z-score: 3.17±1.32) were compared to 31 (58.6% females) normal weight controls (mean BMI z-score:-0.13±0.60). The Child Behavior Checklist [CBCL] was used to evaluate children's IS and ES. Appropriate questionnaires were completed by parents and children. Salivary samples were collected serially 5 times a day. Cortisol was measured by electrochemiluminescence.
Results: T-scores (age and sex specific) of IS reported by children were significantly higher (p=0.03) in the obese than in the lean children (49.3±12.3 *vs.* 43.2±9.1, respectively). The same was observed in the mothers' reports (p< 0.001, 60.6±11.3 *vs.* 50.6±10.4). ES reported by mothers were significantly higher (p=0.003) in obese children than in controls (T scores: 57.2 ±10.5 *vs.* 48.2±13.3, respectively), which was not confirmed by children´s reports. The cortisol area under the curve was significantly smaller in the obese children than the controls (p=0.03). A cortisol correlation with IS/ES was not observed in the analysis however.
Conclusions: There is a high prevalence of internalizing and externalizing symptoms in obese children. Daily salivary cortisol was lower in obese than in control children, suggesting a prevailing pattern of atypical depression.

LB2-1500 Fat Metabolism, Obesity

Interrelations between serum N-terminal pro B-type natriuretic peptide (NT-proBNP) levels and early cardiovascular risk factors and echocardiographic parameters in obese adolescents

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Objective and hypotheses: This study aimed to evaluate the associations between the N-terminal pro B-type natriuretic peptide (NT-proBNP) levels and the metabolic, echocardiographic parameters, carotid intima-media thicknes (IMT) and epicardial adipose tissue thickness (EATT) in adolescent obesity.
Methods: The study participants consisted of 138 obese adolescents in the study group and 63 non-obese adolescents as control subjects. All the subjects underwent transthoracic echocardiographic examination for determination of left ventricular (LV) systolic function and mass index, myocardial tissue rates, and myocardial performance index (MPI). Epicardial adipose tissue thickness and carotid IMT were also measured during echocardiography. Serum NT-proBNP levels were measured at the time of the evaluation.
Results: The NT-proBNP values averaged 67.2 ± 64.4 pg/ml in mildly-moderately obese and 76.0 ± 49.7 pg/ml in the severely obese group and 44.3 ± 23.3 pg/ml in the control group (p : 0.007, p : 0.002, respectively). The average carotid IMT was 0.91 ± 0.23 and 0.88 ± 0.18 mm in the obesity groups and 0.52 ± 0.08 mm in the control group (p : 0.0001), but differences were not observed between obesity groups and the EATT which averaged 7.38 ± 1.76 and 7.42 ± 1.55 mm in the obesity groups and 4.28 ± 0.79 mm in the control group (p : 0.0001). The NT-proBNP levels showed statistically significant positive correlations with left ventricular systolic and diastolic functions, carotid IMT, or EATT values especially in severely obesity.
Conclusions: The study showed higher measurements of serum NT-proBNP levels in mildly-moderately and severely obese adolescents than control and NT-proBNP might be useful marker for predicting atherosclerosis and cardiac dysfunction in obese adolescent.

LB2-1501 Fat Metabolism, Obesity

Long-term treatment of n-3 polyunsaturated fatty acids in obese children with non-alcoholic fatty liver disease

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Aim: To investigate the efficacy and safety of n-3 polyunsaturated fatty acids (PUFA) from seal oils in obese children with nonalcoholic fatty liver disease (NAFLD).

Methods: 108 children (9-17 years old) with NAFLD were included in the 12-mo, randomized, controlled trial. The patients were randomized into two groups. Group I (n=52) received recommended diet plus placebo and lifestyle intervention. Group II (n=56) received diet plus 1 g n-3 PUFA and lifestyle intervention from seal oils, one times a day.
Results: After 12 months later, there was a significant decline in body mass index, fasting insulin and homeostatic model assessment (HOMA) values in two groups. After diet plus placebo and lifestyle intervention treatment, 21 (40.3 %) patients had a decrease from baseline in the prevalence of steatosis (p=0.04) and the prevalence of elevated serum ALT from 38.4 % (n:20) to 28.8 % (n:15) and elevated serum AST from 30.7% (n:16) to 28.8% (n:15) (p:0.01, p>0.05, respectively). After diet plus lifestyle intervention and n-3 PUFA treatment, 67.8 % (n:38) patients had a decrease from baseline in the prevalence of steatosis (p< 0.001) and the prevalence of elevated serum ALT from 39.2 % (n:22) to 14.2 % (n:8) and elevated serum AST from 25 % (n:14) to 17.8 % (n:10) (p< 0.01, p:0.01 respectively).
Conclusion: Our results indicate that n-3 PUFA from seal oils is safe and efficacious in obese children with NAFLD and can improve their ALT, AST, serum insulin and lipid levels and ultrasonographic evidences.

LB2-1502 Fat Metabolism, Obesity

Paediatric providers are poor at identifying severe obesity in young children

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Background: Severe obesity affects even young children. Identification of obesity in toddlers and preschool-aged children is critical for early lifestyle interventions and preventing future metabolic complications. Recognition of obesity in older children using ICD-9 codes or clinical documentation has been shown in previous studies to be poor. Appropriate recognition and documentation of severe obesity in young children has not been studied.
Objective and hypothesis: To determine the extent in which severe obesity (BMI ≥ 99th percentile) in young children is recognized appropriately by pediatric providers in a tertiary medical center. We hypothesized that documentation of obesity status in this age group would be poor.
Methods: 2420 children ages 1-5.99 years with a BMI ≥99th percentile (by WHO and/or CDC growth curves) were identified (1/2010 to 6/2012). After excluding diagnoses that promote weight gain, 1237 patients were reviewed with natural language processing (NLP) to identify weight-related terms in notes. ICD-9 codes were also captured.
Results: 418/1237 (33.8%) of patients were identified by a provider as having excess weight determined by either NLP or weight-related ICD-9 codes. Out of those, 63% were accurately labeled as "obesity," "BMI ≥ 99th percentile," or "severe obesity." The remainder were identified as "overweight," "heavy," "abnormal weight gain," or "large weight for height." Thus out of the total 1237 patients with severe obesity, only 267 (21.6%) were both identified and correctly labeled in the chart.
Conclusions: These results suggest that providers are poor at identifying obesity in children under 6 years old. Even when identified, our results indicate that the severity of the weight status may not be appropriately recognized. Identification and treatment of obesity in the young child is critical as these children have a high risk of life-long complications from excess weight.

LB2-1503 Fat Metabolism, Obesity

Plasma obtained from prepubertal severely obese children modifies insulin stimulated nitric oxide (NO) bioavailability in cultured human umbilical vein endothelial cells (HUVECs)

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Background: Childhood obesity is commonly associated with initial endothelial dysfunction where decreased NO bioavailability seems to be involved. Recently, the Endoplasmic Reticulum (ER) stress has also been associated with the impairment of insulin signaling and vascular NO availability, but its potential role in mechanism/s leading to vascular dysfunction in obesity is poorly understood.
Objective and hypothesis: To evaluate ER-stress and insulin-stimulated NO availability in HUVECs cultured with plasma obtained from severely obese (OB) and normal-weight (C) prepubertal children.
Methods: Plasma were obtained from OB- (N=6, age: 10.0±1.0 yr; BMI SDS: 2.27±0.27) and C-children (N=6, age: 9.7±1.1 yr; BMI SDS: 0.02±0.26). Fasting insulin and glycaemic levels were measured. HUVECs were cultured for 72 hrs with 10% plasma, insulin (100 nM) was added during the last 24 hrs to determine: HUVECs viability (MTT analysis); eNOS activity (conversion of L-[3H]-arginine into L-[3H]-citrulline) and NO bioavailability (intracellular cGMP levels by EIA). Twenty-four hrs plasma effects on GRP-78 and NF-kB, respectively ER-stress and inflammatory markers, were quantified by flow cytometry analysis.
Results: OB-children presented higher fasting insulin levels (20.7±7.6 vs 5.6±1.8 mU/ml, p< 0.05) in the context of normal fasting glycaemia (86±6.0 vs 82.2±9.3 mg/dL; p>0.05) when compared to C-children. Insulin increased respectively 3 and 1.2 folds eNOS activity and cGMP levels in HUVECs treated with C-plasma, whereas it was uneffective in OB-plasma treated cells. Moreover, compared to controls, stimulation with OB-plasma significantly increased GRP-78 (0.8±0.1 vs 1.2±0.2 MFI ratio, p< 0.05) and NF-kB (1.2±0.1 vs 1.9±0.4 MFI ratio, p< 0.05) levels in HUVECs.
Conclusions: Taken together our in vitro data demonstrate that plasma from obese children are able to reduce endothelial insulin sensitivity and this may be associated with increased ER stress and inflammation.

LB2-1504 Fat Metabolism, Obesity

The effect of childhood obesity on cardiac functions

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Background: Obesity is a metabolic disorder defined as excessive accumulation of body fat which is made up of genetic, environmental,hormonal factors and has various social, psychological and medical complications. Childhood obesity is a major indicator of adult obesity.
Aim: The aim of this study is to evaluate the cardiac functions via electrocardiography, echocardiography and treadmill test in childhood obesity.
Methods: A patient group consist of 30 obese children and a control group consists of thirty non-obese children was included to the study. The age range was between 8 and 17 years. Anthropometric measurements, physical examination, electrocardiography, echocardiography and treadmill test were done in all patients. P wave dispersion was found to be statistically significant high in obese patients.
Results: In echocardiography analysis, we found that end diastolic diameter, end systolic diameter, posterior wall thickness of left ventricle and interventricular septum was significantly greater in obese children. In treadmill

test, the exercise capacity was found to be significantly lower and the hemodynamic response to exercise was found to be defective in obese children. Various cardiac structural and functional changes occur in childhood obesity and this condition includes important cardiovascular risks. P wave dispersion, left ventricle end systolic and end diastolic diameter, left ventricle posterior wall thickness, interventricular septum thickness, exercise capacity, hemodynamic and electrocardiographic measurements during exercise testing are useful tests to determine cardiac dysfunctions and potential arrhythmias even in early stages of childhood obesity.
Conclusion: Early recognition and taking precautions of obesity during childhood is very important to intercept complications that will occur in adulthood.
Keywords: Childhood, obesity, cardiac functions

LB2-1505 Fat Metabolism, Obesity

The new effect of growth differentiation factor 5 on 3T3-L1 preadipocyte differentiation

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Background: Adipocyte differentiation is key to determining the number of adipocytes that mature during the development of obesity.
Objective and hypotheses: The purpose of the present study was to investigate the effect of GDF5, a member of the transforming growth factor-β (TGF-β) superfamily involved in chondrogenesis and skeletalgenesis, on adipocyte differentiation and obesity.
Methods: The differentiation of 3T3-L1 preadipocytes was induced by MDI (IBMX, Dex and Ins) or MD (IBMX and Dex). The mRNA levels of PPARγ, C/EBPα, C/EBPβ, aP2 and Adiponectin were detected by real-time PCR. Cell cycles were analyzed by flow cytometry after treating by MDI for 16h and 24h. Three shRNAs were designed to knockdown the expression of GDF5 gene in 3T3-L1 preadipocytes. After shRNA intervention, the differentiation of 3T3-L1 cells inducing by MDI and the expression of the genes related to adipocyte differentiation was detected.
Results: GDF5 was found to increase the rate of differentiation of 3T3-L1 preadipocytes, especially when exposed to hormone cocktails not containing insulin. During adipogenesis, GDF5 enhanced expression of genes related to adipocyte differentiation and caused cells to enter the S phase. However, short-hairpin-RNA knockdown of GDF5 in 3T3-L1 cells was found to prevent adipogenesis induced by a standard hormone cocktail and to downregulate the expression of genes and proteins.
Conclusions: These results suggest that GDF5 may play critical role on the middle and late adipogenic gene expression during 3T3-L1 preadipocytes differentiation.

LB3-1506 Glucose Metabolism

Abstract has been withdrawn

LB3-1507 Glucose Metabolism

Are paediatric patients attending their annual diabetic retinopathy screening?

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Background: Glycaemic control and longer duration of diabetes mellitus plays a role in delaying or preventing diabetic retinopathy. NICE guidelines state those with type 1 diabetes aged 12 years and over must be offered annual retinopathy screening.
Objective and hypotheses: Diabetic retinopathy screening is performed locally, annually. We aim to assess compliance with NICE guidelines and explore the prevalence of retinopathy.
Methods: This was a retrospective audit of paediatric diabetic patients registered to Good Hope Hospital attending diabetic retinopathy screening in 2011 and 2012. Data was obtained from Retinal screening co-ordinators and the Optimize database. All children aged 12 at the start of the screening year with type 1 or type 2 diabetes were included. Data collected included: demographic, screening attendance and results, HbA1c, and duration of diabetes.
Results: In 2011, of 79 eligible paediatric patients, 49 (62%) attended screening. 10 (20.4%) patients had stage 1 retinopathy. Patients with retinopathy had a higher mean HbA1c (9.6mol/L vs 9.3mmol/L) and longer duration of diabetes (8.6 years Vs 5.8 years, p value< 0.05). In 2012, of 91 eligible paediatric patients, 63 (69.2%) attended their annual retinopathy screening. 14 (22.2%) patients had stage 1 retinopathy. Patients with retinopathy had a higher mean HbA1c (9.9mol/L vs 9.5mmol/L) and a longer duration of diabetes (7.9 years Vs 5.5 years, p value < 0.05).
Conclusions: Glycaemic control varies widely within this cohort, but on average is higher than recommended target levels in patients both with and without retinopathy. Longer duration of diabetes is significantly associated with retinopathy, and there is a trend towards an association with higher HbA1c levels. Retinal screening uptake in the community may be improved by patient education and better communication with primary care. Suboptimal glycaemic control may be improved by intense insulin regimens and structured education programmes.

LB3-1508 Glucose Metabolism

Diabetes mellitus type 1 and 25(OH)vitaminD levels in children and adolescents

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Background: Vitamin D is important for bone health and its deficiency is common. Patients with diabetes type 1 are reported to have lower levels and higher fracture risk.
Objectives and hypotheses:To compare serum levels of 25(OH)vitamin D between type 1 diabetic patients and healthy controls; To look for correlations between its level and disease duration, metabolic control and insulin dose.
Methods:A cross-sectional study of 73 patients (35 males)aged 11,3±4,1 yrs and 23 healthy controls (12 males)aged 7,3± 4,7 yrs.They are divided in 4 groups according to disease duration: new; 6 months-5 yrs; 5-10 yrs;>10 yrs. Those with evolution >6 months are divided according to metabolic control: optimal (HbA1c ≤ 7,5%) and unsatisfactory (HbA1c > 7,5%). Serum levels of 25(OH)vit D examined by electrochemiluminescence,HbA1c - immunoturbidimetric method.US Endocrine Society guideline is used to define vitamin D status.Statistical analysis-SPSS 15.0.
Results: Mean level of 25(OH)vitamin D in controls is 27,63 ±9,74 ng/ml, in patients- 25,39±8,14 ng/ml (p>0,05). 35% of patients (n=26) and 21% (n=5) of controls have vitamin D deficiency. Vitamin D insufficiency is observed in 37% of patients (n=27) and in 43% of controls (n=10).
Duration of diabetes is 0,04±0,1 yrs (n=15); 2,4±1,4yrs (n=27); 7,1±1,5yrs (n=24) and 10,7±0,6yrs (n=7). The corresponding levels of 25(OH)vit D are: 23,7±9,2ng/ml; 26,9±7,6ng/ml; 25,5±8,7ng/ml and 22,9±5,9ng/ml (p>0,05). Mean levels of HbA1c are:optimal group-6,98%±0,4;unsatisfactory group-9,2%±1,4. 25(OH)vit D is 25,95±7,26 ng/ml and 25,69±8,30 ng/ml respectively (p>0,05).No correlation with metabolic control is found.
Mean insulin dose is 0,91 ±0,3U/kg without correlation with 25(OH)vit D(r=0,019, p=0,845).
Conclusions: Presence of diabetes mellitus type 1 does not influence vitamin D metabolism. Level of 25(OH)vitamin D is not dependent on disease evolution, metabolic control and insulin dose.

LB3-1509 Glucose Metabolism

European research network in diabetes and endocrinology

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Representatives from ESPE and ISPAD have had a series of meetings facilitated by the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) to discuss the establishment of a European children and adolescent Diabetes and Endocrine Research Network.

Aims:

• To develop research infrastructure across the EU within the field of diabetes and endocrinology.

• To work with Industry in the development and implementation of full Paediatric Investigational Plans (PIPs).

• To work with academia to promote drug development in rare paediatric endocrine disorders

• To collaborate with the European Medicines Agency Paediatric Committee (EMA PDCO) in designing strategies for drug development.

Stakeholders:

• Academic paediatricians

• Industry

• Patient groups

• ESPE

• ISPAD

Specific studies in type 2 Diabetes:

• Collaboration of multi-company, multi-agent academic led, pharma-funded, Clinical Research Organisation (CRO) managed trials.

• Post-marketing surveillance of all new type 2 diabetes products

We encourage all national paediatric endocrine and diabetes groups to engage with this exciting project.

LB3-1510 Glucose Metabolism

Glycaemic variability in type 1 diabetes: which indicators to use?

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Background: GV is an important parameter of metabolic control in T1D patients. It is a risk factor for significant glucose excursions, especially hypoglycemia, and suspected as involved in the pathogenesis of vascular complications regardless of HbA1c. The association with the alteration of quality of life in T1D patients is also mentioned. Many indicators of GV are available; however, there is no consensus on their practical use.

Objective: To identify the best indicators of glycemic variability, both for clinical practice and as the endpoints for clinical trials.

Methods: The population is derived from a randomized clinical trial (Start-In!) which assesses the impact of continuous glucose monitoring (CGM) on HbA1c in T1D children and adolescent. During the first 3 months, 141 subjects were wearing a CGM device for more than 90% of the time. Fifteen GV indicators were calculated weekly during these 3 months (BG mean; SD; coefficient of variation-CV; Mean Amplitude of Glycemic Excursion-MAGE; Mean Of Daily Difference-MODD; Continuous Overall Net Glycemic Action-CONGA 1, 2, 4 and 24; J-index; M-Value; GRADE; Low Blood Glucose Index-LBGI; High Blood Glucose Index-HBGI; Average Daily Risk Ratio-ADRR). Indicators were analyzed using principal component analysis (PCA) and Spearman's correlations.

Results: Three components of the GV were highlighted, possibly representing variability per se, magnitude (hypo/hyperglycemia), and temporality (intra/interday) of glycemic excursions. Each of these components explains respectively 66%, 18%, and 5%, in total 89% of the variance. Spearman's coefficients inside each group of indicators defined by the PCA, greater than 0.70, reinforce the first results. Thus, 6 indicators appear sufficient to fully describe GV: 3 descriptive parameters (MAGE MODD, CV) and 3 risk indicators (LBGI, HBGI, ADRR).

Conclusion: Six among 15 GV indicators are able to evaluate the 3 GV dimensions and should be used as standardized outcomes in clinical trials.

LB3-1511 Glucose Metabolism

Insulin independence after fetal hematopoietic stem cells allotransplantation in patients with type 1 diabetes

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Background: Cell therapy is considered as one of the most promising potentially curative treatment for type 1 diabetes. In this regard, various strategies including islet transplantation, obtaining beta cells from stem cells as an alternative source of islets, using porcine islets, and beta cell expansion with growth factors have been examined.

Objective and hypotheses: The aim of this study is to examine the outcome after treatment with fetal hematopoietic stem cells in patients with type 1 diabetes

Methods: 18 patients with type 1 diabetes aged 6-40 years were included in the study. Each patient received fetal liver derived hematopoietic stem cells intravenously from legally aborted early human fetus aged 6 -12 weeks. The patients were followed up for 2 years and their plasma glucose as well as HbA_1C levels were monitored over this period.

Results: Blood glucose levels gradually decreased within the first day of the treatment in 5 out of 18 patients. Daily insulin requirement of these 5 patients was (0.35-0.70 u/kg/day) which decreased significantly after the intervention. 2 patients out of the 5 remained constantly insulin free for 16 and 24 months. In the other patients, no significant changes in the course of their disease were observed

Conclusions: : the findings of the current study demonstrated that fetal hematopoietic stem cell transplantation in patients with type 1 diabetes was partially successful in the treatment diabetes. Moreover, the observation that no immunosuppressive agents before and after the transplantation was necessary because of the low immunogenicity of fetal hematopoietic stem cells, adds to the value of this new therapeutic modality. However, further clinical trials with larger number of patients and long term follow- ups would be useful to confirm the efficacy and safety of the procedure.

LB3-1512 Glucose Metabolism

Insulin resistance in adolescent girls with PCOS

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Background: PCOS is a complex, heterogeneous, and one of the most common endocrine disorders in female, and is often in adolescence. PCOS defined by the presence of 2 of the 3 criteria: polycystic ovaries on ultrasound, oligomenorrhea or chronic anovulation, and clinical and biochemical hyperandrogenism. Many studies suggest that the clinical expression of PCOS significant associated with resistance to insulin.

Objective and hypotheses: To determine the presence of specific clinical symptoms of PCOS, as well as the incidence of metabolic syndrome in adolescent girls with PCOS.

Methods: 16 adolescents girls (11.8 to 17.5 years) treated at the Department of Pediatrics Clinic in Kragujevac, which was diagnosed PCOS and verified the presence of the metabolic syndrome according to current criteria: Rotterdam Consensus Criteria, 2003., or presence of ≥ 3 criteria for the metabolic syndrome (MS) in children and adolescents: (IDF, 2007). Standard OGTT was conducted and interpreted according to the current WHO criteria
Results: Of the 16 adolescents, 6 (37.5%) were obese (mean BMI 32.6 kg/m^2, > p97), 5 (31.2%) overweight (mean BMI 27.3 kg/m2, p90-95) and 5 (31.2%) of normal weight (mean BMI 22.6 kg/m/2, p10-25). Polycystic ovaries on ultrasound were seen in all girls, in 12 (75%) was determined hirsutism, 11 (69%) oligomenorrhea, 5 (31%), amenorrhea, and 9 (56%) acanthosis nigricans. In the girls were determined mean values of testosterone 82.1 ng/dl, free testosterone, 2.15 pg/ml, SHBG 24.9 mmol/l, and DHEAS 2250ng/ml. In 2(12.5%) obese girls was diagnosed DM, in 4 (25%) IGT, and impaired fasting glucose (IFG) had 2 adolescents (12.5%). Metabolic syndrome was diagnosed in 5 (31.2%) of investigated girls. Positive family history of DM had 7 (43.7%) girls, and 6 (37.5%) mothers had PCOS.
Conclusions: : The high prevalence of metabolic syndrome, obesity and glucose intolerance of the surveyed girls calls for routine evaluation of insulin sensitivity in adolescents with PCOS.

LB3-1513 Glucose Metabolism

NGAL: an early marker of diabetic nephropathy?

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Background: Diabetic nephropathy (DN) is one of the most severe complications of type 1 diabetes (T1D) and until nowadays its early diagnosis is based on microalbuminuria (MA),
Objective and hypotheses: In this study we aimed to explore the use of new biomarkers of renal injury, such as neutrophil gelatinase-associated lipocalin (NGAL) and Cystatin C(CysC) for the early identification of DN in young patients with T1D.
Methods: 60 T1D patients, aged 5-21, are included in this prospective cross-sectional study. Along with standard blood and urine chemistry, serum NGAL levels by means of immunoenzymatic assays and serum levels of CysC by nephelometry were measured twice in a time interval of 12-15 months. GFR was calculated with the Schwartz bedside formula(eGFR) and the more recently suggested by Schwartz et al. eGFR- formula with CysC(CysC eGFR).
Results: NGAL is found to correlate negatively with the eGFR and CysC eGFR(p=0.05, r=-0.25 and p = 0.01, r = -0.33, respectively)**.** It was also positively correlated to CysC(p=0.0005, r=0.49), the systolic arterial pressure(SAP)(p=0.004, r=0.39) and the serum Creatinine(sCr)(p= 0.01 r=0.34). The mean value of NGAL was increased at the measurement performed 12-15 months after the baseline(p=0.03). The CysC is found to have a negative correlation to the eGFR(p= 0.03, r=-0.2) and was positively correlated to sCr(p=0.006, r=0.37). Neither NGAL nor CysC concentrations were correlated with the Tanner stages of puberty of the participants.
Conclusions: NGAL and CysC, known markers of renal injury, are found to correlate with the renal function decline in T1D patients suggesting that they may be early markers of DN. The fact that they do not correlate with pubertal Tanner stages implies that they are not influenced by hormonal factors intervening during puberty. These findings suggest that early assessment of these markers may unmask the endothelial dysfunction in T1D patients before overt MA and renal impairment become obvious.

LB3-1514 Glucose Metabolism

Screening for coeliac disease in children diagnosed with diabetes mellitus

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Background: Coeliac disease has higher prevalence in children with diabetes mellitus than in the general population, and can have significant impact on quality of life causing faltering growth, prolonged fatigue and recurrent abdominal pain.
Objective and hypotheses: To compare current practice in screening for coeliac disease in children with diabetes mellitus with recommended standards and to investigate the value of follow-up screening for coeliac disease in children previously diagnosed with diabetes mellitus.
Methods: 146 children under 19 years old who had been diagnosed with diabetes mellitus were retrospectively included. Results of coeliac screening at diagnosis (IgA Anti-TTG) and annual coeliac screening were analysed. Case notes of children who had positive results were analysed to see if symptoms were documented. Children with positive antibodies were referred to tertiary hospital and biopsy undertaken. Positive biopsy was taken as gold standard for diagnosis.
Results: We found the prevalence of coeliac disease at diagnosis to be 5%. Of the remaining 109 patients who had routine regular follow-up screening, 14 were serology positive out of which 6 were diagnosed with coeliac disease after biopsy. 3 were symptomatic.
Conclusions: We recommend routine continued surveillance screening for coeliac disease after the diagnosis of type 1 diabetes in children.

LB3-1515 Glucose Metabolism

Screening glucose disorders in cystic fibrosis: continuous subcutaneous glucose monitoring compared to oral glucose tolerance test

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Background: Diabetes is an important complication of cystic fibrosis (CF). It is associated with increased morbidity and, if left untreated, can lead to deterioration of nutritional and pulmonary status.
Objective and hypotheses: The aim of this study was to evaluate the glycemic profile with continuous glucose monitoring system (CGMS) in patients with CF followed in a terciary pediatric center, and compare these results with oral glucose tolerance test (OGTT) and HbA1c.
Methods: Patients selected performed CGMS during five days, were submitted to OGTT and was measured HbA1c. Patients younger than 10 years, with current corticosteroids or immunosuppressive treatment and those who were transplanted or who already had the diagnosis of diabetes were excluded.
Results: Nine patients were included, five males, with a mean age of 17,8 years. Three patients had homozygous ΔF508 CF-mutation. All patients had normal OGTT and a median HbA1c value of 5,4±0,29% [5,1-5,9%]. Mean CGMS glucose was 102,7±8,2 mg/dl and mean glucose lowest and highest values were 63,2±13,7 mg/dl [47-87 mg/dl] and 164,5±27 mg/dl [132-218 mg/dl], respectively.
In seven patients, CGMS showed peaks of glucose higher than 140 mg/dl at least once after a meal and one individual had values above 200 mg/dl despite normal OGTT. We also found asymptomatic hypoglycemias in five patients during CGMS. **Conclusions:** Most patients had a glucose profile during CGMS with values below 200 mg/dl. However, we observed abnormal glucose values in more than half of the patients. Asymptomatic hypoglycemias found in this study may reflect an inadequate insulin secretion. The authors believe that CGMS allows a better diagnosis of glucose disorders in patients with CF compared to OGTT.

LB3-1516 Glucose Metabolism

Structured feedback in the development of the first educational smartphone application (Pumps4Kids) for insulin pump education

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Background: The transition from subcutaneous injections (SI) to continuous subcutaneous infusion pump therapy (CSII) requires extensive education. Increasing smartphone use by children with diabetes may provide an opportunity to support this.
Objective and hypotheses: To describe the process of developing the first smartphone application to enhance pump start education, utilizing patient centered feedback.
Methods: A child centered educational application was developed using a three-stage approach. Patient feedback guided content, using 1) Questionnaires for teenagers using SI, and 2) Daily phone calls for teenagers in the week after commencing CSII. The design and layout of this application utilized feedback from children with diabetes at each stage. Following release, prospective feedback was collected through an integrated feedback mechanism included in the design.
Results: Four fifths of teenagers using SI had smartphones and used the Internet as their main source of diabetes related education. Difficulties identified by new users of CSII in the first week were related to exercise, infusion set changes, hypoglycemia and hyperglycemia. A smartphone application (Pumps4Kids) was developed for Android and iPhone platforms. In the first three months following release, the application was accessed 2079 times in 48 countries.
Conclusions: This is the first educational application developed for children with diabetes aiming to commence insulin pump therapy or enhance their insulin pump use. Problem orientated design and structured feedback played key roles in developing this age-appropriate educational tool for children and teenagers with diabetes. Ongoing feedback will be key to ensuring that this application evolves to meet the needs of children with diabetes.

LB3-1517 Glucose Metabolism

Testosterone levels and lack of hypogonadism in male adolescents and adults with type 1 diabetes

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Background: Men with type 2 diabetes often have decreased testosterone (TT) levels that correlate with age and visceral obesity,but until now there is no clarity regarding the prevalence of hypogonadism in male adolescents (adols) and adults with type 1 diabetes (T1D).
Objective: Assessing levels of total and free TT in men adols and adults with T1D
Hypothesis: Adols and adult men with type 1 diabetes have impaired testicular function reflected by decreased total, free or bioavailable TT.
Population and Methods: Men with T1D(N = 51) and healthy controls (N = 51) aged between 13 and 70 years were studied. They were grouped in adols (Tanner 5,< 20 years old) and adults (>20 years old). Plasmatic TT and SHBG levels were measured. Free TT and free androgen index (FAI) was calculated. Hypogonadism was diagnosed based on total TT levels< 8nmol/L and free TT< 220pMol/L.
Results: No case of hypogonadism was observed in any adult or adols with T1D and C. In T1D men mean HbA1c was 8.5±1.62.There were no differences in HbA1c levels between adols and adults with T1D(8.3±1.39vs8.8±1.73,*p*=0.33). Adols with T1D have higher total TT(517±153vs418±140ng/dl,*p*=0.011), free TT levels (424±138vs334±109ng/dl, *p*=0.007) and FAI (63±50, *p*=0.01) compared with C adols. Adult with T1D have higher SHBG levels (42±15vs31±11nmol/L, *p*=0,015) and lower FAI than C adults(46±16vs59±18, *p*=0.018), but levels of total and free TT were similar in both groups. Adults with T1D have higher SHBG levels(*p*=0.003) and lower FAI than adols with T1D(*p*=0.004), while adult controls exhibit higher levels of total (*p*=0.034) and free TT(*p*=0.03) and similar SHBG compared to controls adols. In T1D adults and adols TT levels did not correlate with age, HbA1c, dose/kg of insulin or BMI.SHBG levels was positively correlated with age and negatively with HbA1c, insulin dose, free TT and FAI.
Conclusions: Hypogonadism was not observed in this series of T1D patients. In T1D patients, metabolic control was associated with SHBG but not TT levels.

LB3-1518 Glucose Metabolism

Transient expressive aphasia and quadriparesis in a patient treated for severe diabetic ketoacidosis

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Introduction: The most common neurological complication of diabetic ketoacidosis (DKA) is cerebral oedema. Ischaemic and haemorrhagic brain injury are reported to a lesser extent.
Case: A 10-year old Chinese girl presented with classical history of diabetes for 2 weeks and vomiting for 2 days. On arrival, she appeared drowsy with acidotic breathing. Glucometer reading showed 'HI' and the blood pH 7.011, bicarbonate 6.4mmol/L. Urinalysis revealed ketonuria and glucosuria. Two boluses of 20mls/kg normal saline were given. She was transferred to another hospital where she was intubated due to drowsiness and restlessness. Her metabolic acidosis worsened (pH 6.959, HCO3 5.5mmol/L). Fluid maintenance and 48-hour correction for 7.5% dehydration (minus boluses) were started followed by insulin infusion. She was extubated the following day. However, on day 2 of admission she had reduced GCS 11/15 (E4M5V2), expressive aphasia with upper motor neuron signs (hypereflexia, hypertonia and quadriparesis). One dose of Mannitol was given. Insulin infusion was converted to basal bolus injection after 48 hours. She was transferred to our center for further management of diabetes and her neurological abnormality. Her symptoms improved and she was discharged with residual left hemiparesis and mild expressive aphasia. Serial MRI brain was highly suggestive of vascular ischaemic injury at the water shed regions with haemorrhagic transformation. Differentials include haemorrhagic leucoencephalitis or vasculitis, but her inflammatory markers were negative. When seen as an out-patient 6 weeks later her speech fully recovered, with only minimal residual left lower limb paresis.
Conclusion: Judicious bolus administration and correction of dehydration is vital to ensure optimum DKA management. In addition, patient's neurological status must be closely monitored to detect any neurological impairment.

LB4-1519 Pituitary, Growth and Thyroid

CUL7, OBSL1 and CCDC8 modulate alternative splicing of exon 11 of the insulin receptor gene

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Background: The primordial growth disorder 3-M syndrome is caused by mutations in *CUL7*, *OBSL1* and *CCDC8* and we have associated these proteins with mRNA splicing machinery including the heterogeneous nuclear ribonucleoprotein (HNRNP) complex. Insulin is important to fetal growth, and insulin resistance in later life is associated with being born small. The insulin receptor (INSR) is alternatively spliced in a developmental and tissue specific manner to give rise to two isoforms, IR-A and IR-B. IR-A excludes exon 11 and is widely expressed whereas IR-B includes exon 11 and is expressed in insulin sensitive tissues.
Objective and hypotheses: To determine if 3-M proteins are involved in the regulation in *INSR* splicing.

Methods: We co-transfected expression vectors for the 3-M genes and an *INSR* minigene (containing intronic and exonic sequence between exons 10-12) into HEK293 cells, the minigene was also transfected into control and 3-M patient fibroblast cells. Analysis of exon 11 splicing was determined by RT-PCR and alteration of the ratio of IR-B/IR-A by gel densitometry.
Results: Over-expression of the 3-M genes in HEK293 cells caused a decrease in exon 11 inclusion (increase in IR-A) and a reduction in the IR-B/IR-A ratio ($p < 0.001$). While reduced expression of 3-M genes in patient cells caused an increase in exon 11 inclusion (decrease in IR-A) and therefore an increase in the IR-B/IR-A ratio ($p < 0.001$).
Conclusions: Alternations in *INSR* splicing have been associated with HNRNP proteins. We now demonstrate that the interaction of the 3-M proteins with these splicing proteins modulates exon 11 splicing. The alteration of IR-A expression in response to changes in 3-M gene expression may in part explain the reduced growth seen in 3-M patients as IR-A predominantly mediates the mitogenic effects of insulin. However the changes in the IR-B/IR-A ratio may also play a role in insulin resistance associated with being born small.

LB4-1520 Pituitary, Growth and Thyroid

Growth proportions, obesity and hypertension in children: what is the relation?

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Background: The decomposition of statural growth in terms of proportions between superior and inferior segments is one of the most common ways of analyzing growth proportions and has been used as an important auxological parameter in the work-up of children with growth disorders.In adults, relatively short members have been associated to higher rates of metabolic disorders and adverse cardiovascular outcomes. Few studies have addressed this question in children.
Objective: To evaluate the relationship between body proportions and the presence of obesity and hypertension in children.
Methods: 817 children aged 6 to 13 years were evaluated. Weight, height, sitting height (SH), sitting height to height (SH/H), body mass index (BMI) and blood pressure (BP) levels were assessed and converted to standard deviation scores (SDS) adjusted for age and sex. Association analyses were carried out using comparisons, correlations and linear regressions.
Results: There was a positive association of BMI SDS with SH SDS ($p < 0,001$, $R^2 = 0,22$) and SH/H SDS ($p < 0,001$, $R^2 = 0,02$). Children with overweight or obesity presented SH, on average, 0,8 SDS superior to normal weight children ($p < 0,001$)**.** Moreover, SH SDS was directly related to waist circumference ($p < 0,001$) and BP levels SDS. Nevertheless, multiple linear regressions showed that this correlation was not independent on the strong association between obesity and BP levels.
Conclusions: Children who are overweight or obese tend to have relatively long trunk when compared to members, which may interfere in the interpretation of SH/H values. The exact cause of this association and the possible relationship with other metabolic risk factors need to be further evaluated. The association between SH and blood pressure levels is not independent on the association of these variables with BMI; and a possible confounding bias may be related to previously described associations.

LB4-1521 Pituitary, Growth and Thyroid

Long-term safety and effectiveness of daily and once-weekly growth hormone treatment in paediatric patients

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Background: Daily and Once-weekly Growth hormone (GH) have been used to treat growth disorders in children, including growth hormone deficiency (GHD), turner syndrome (TS), chronic renal failure (CRF), small for gestational age (SGA) and idiopathic short stature (ISS). However, there is still a lack of sufficient real-world data of daily and once-weekly GH among Korean patients.
Objective and hypotheses: To evaluate the long-term safety and effectiveness of two formulations of GH (daily (Eutropin inj.) and once-weekly (Eutropin Plus inj.)) in Korean pediatric patients.
Methods: An open, multi-center, prospective, retrospective and long-term cohort study. The statistical analysis will continue to be conducted annually using a pre-defined method. The first interim analysis was conducted in all patients who were enrolled from Jan 2012 to Mar 2013. All patients were diagnosed with either GHD, TS, CRF, SGA or ISS. 858 patients, 428 males and 430 females, mean aged 8.78 year.
Results: Mean height SDS increased during the first year after GH treatment by 0.59 and 0.50 in daily and once-weekly, respectively, and the difference from baseline was statistically significant within the groups. Mean height velocity was 8.40 cm/year and 8.12 cm/year in the two groups, respectively. Mean height SDS and velocity were similar amongst the two groups. Adverse events were reported in 9.79% of daily and 10.61% of once-weekly. Serious adverse events occurred in 0.19% of daily with none reported in the once-weekly group.

	Daily (n = 221)	Once-weekly (n = 54)	p-value
Height SDS at Baseline	-2.44±1.03	-2.63±1.03	0.2388
Height SDS at 1 year	-1.83±0.92	-2.13±1.12	0.0419
Change from baseline	0.59±0.44	0.50±0.54	0.2682
p-value (Baseline vs. 1 year)	<0.0001	<0.0001	
Height velocity (cm/year)	8.40±2.55	8.12±2.38	0.4557

[Table 1. Effectiveness results at the first year a]

Conclusions: Height SDS and velocity have shown to be significantly improved during the first year after GH treatment in pediatric patients. Adverse Events in both groups were similar to other historical registry studies. Both daily and once-weekly formulations were comparable in safety and effectiveness. Further long-term follow-up study will be conducted to secure more extensive data on the safety and effectiveness of both daily and once-weekly GH.

LB4-1522 Pituitary, Growth and Thyroid

Short stature likely caused by biologically inactive growth hormone (BIGH): auxologic, laboratory and recombinant human growth hormone (GHr) treatment aspects of a collection of 19 patients followed in the period of 1996-2013

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Background: Short stature (SS) with normal GH immunoreactivity but reduced biopotency has been suggested, but the molecular abnormalities have been characterized in relatively few patients. Low IGF-1 levels, normal GH values and catch-up growth on GHr therapy is the hallmark of this entity.
Objective: To report clinical, laboratory and auxologic phenotype of patients with BIGH, before and after GHr therapy.
Methods: Retrospective review of medical records of 19 children and adolescents followed in the period of 1996 to 2013. The following parameters were gathered: birth weight and length, chronological and bone age (CA and BA) at start of GHr; GH (ng/mL) peak values on clonidine and ITT, IGF-1 values (ng/mL) on IGF-1 generation test, GHr dose (mg/Kg/d), target height-SDS (TH-SDS), baseline height-SDS (H-SDS-B) and at 1st and 2nd years (H-SDS-1 and H-SDS-2, respectively) of GHr, baseline height velocity-SDS (HV-SDS-B), and after 1 and 2 years (HV-SDS-1 and HV-SDS-2) of GHr, and final height-SDS (FH-SDS). Values are given as mean ± SD.
Results: Out of 1133 patients with SS treated with GHr 19 (0.016 %) met the criteria for BIGH. Fifteen were males; 17 were born at term;11 were AGA and 7 were SGA; at start of GHr, CA was 9.4±3.8 and BA 7.3±3.2 ($p< 0.001$); GH peak on clonidine and ITT were 19.9±9.3 and 15.6±5.01 respectively; IGF-1 values were 59.9±34.1 and 172.7±98.6 ($p< 0,001$); GHr dose was 0.04±0.01. H-SDS-B (-2.5±1.1) was smaller than TH-SDS (-0.73±1.4, $p=0.003$) and H-SDS-1 (-2.2±0.8) and H-SDS-2 (- 1.6±0.7) ($p< 0.001$); HV-SDS-B (-0.66±2.0) was smaller than HV-SDS-1 (3.9±2.3) and HV-SDS-2 (2.1±2.6) ($p< 0.001$). FH-SDS of 6 patients was -1.3±1.1 whereas their H-SDS-B was -3.0±0.6 ($p< 0.009$).
Conclusions: The prevalence of BIGH among children treated with GHr for SS at a Brazilian Paediatric Endocrinology Center is the first yet reported. GH bioactivity and molecular studies are required to better understand the pathophysiology of SS in these patients.

LB4-1523 Pituitary, Growth and Thyroid

Mild traumatic brain injury and immediate hypopituitarism in children

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Aims: Traumatic brain injury is a common and costly trauma that may lead to hypopituitarism. Its complications may have great impact on public health, especially in children. This study evaluates the prevalence of immediate hypopituitarism in children who suffered mild traumatic brain injury.
Methods: Children who were admitted in the emergency service of Unidade Regional de Emergência - Conjunto Hospitalar de Sorocaba due to traumatic brain injury were evaluated for the study. Every patient underwent a head computed tomography at admittance and was classified according to the Glasgow Coma Scale, being traumatic brain injury graded in severe (< 9), moderate (9-12) or mild (>12). Those whose parents or guardians agreed to participate and presented mild trauma were included in the study and invited to perform a neuroendocrinological evaluation.
Results: Sixty-eight children were admitted with traumatic brain injury, and 21 agreed to participate. Five patients did not perform the urine and blood exams, two had a moderate TBI, and one had a severe TBI, and therefore were excluded from data analysis. Among the 13 patients whose exams were performed in less than 48 hours from the trauma, five (38.5%) presented hormonal alterations, respectively: single thyroid-stimulant hormone (TSH) elevation, single insuline-like growth factor 1 (IGF-1) elevation, single cortisol elevation, combined folicule-stimulant hormone (FSH) and prolactin elevation, and combined TSH and FSH elevation. None presented symptoms of hypopituitarism. There was no association between head image alterations and hypopituitarism.
Conclusions: The results found in this study lead to probably little significant endocrine dysfunctions, as such hormonal increases may be related to acute trauma response. Considering the literature and the results, it is possible to speculate that the relationship of traumatic brain injury with hypopituitarism in children is different from adults.

LB4-1524 Pituitary, Growth and Thyroid

Cavernous sinus sampling and cytology is helpful in pituitary surgery of difficult paediatric Cushing´s disease

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Background: Bilateral inferior petrosal sinus sampling of ACTH is not sufficiently reliable to localize small pituitary adenomas in children with Cushing, as found by Batista (2006) in a large paediatric series. Localization is important for surgical outcome. There is little experience with cavernous sinus sampling (CSS) in children.
Objective and hypotheses: For anatomical reasons, direct bilateral CSS should result in more reliable pituitary ACTH gradients. Complete, selective adenoma resection is especially important for young patients to preserve pituitary function.
Methods: Decision for surgery is based on the triad of positive ACTH, CRH-Test and high dose Dexamethasone test. Since1985 we acquired experience with direct intra-operative CSS. In 1999 the CSS catheter technique of Teramoto (1993) was introduced by our neuroradiologists. Since then, we decided for pre-operative CSS in 7 of 45 (16%) children with unclear MRI. Three had failed primary surgery. All 45 had transnasal surgery by one neurosurgeon. Pre-operatively the cavernous sinus was canulated bilaterally from one femoral vein for central ACTH-gradients to compare with peripheral levels and between both sides. After obtaining CSS gradients under anesthesia, two patients were immediately operated. Three children with negative exploration elsewhere, had intra-operative CSS.
Results: CSS showed high central-peripheral ACTH-gradients in all 10 patients. In 9, including 3 direct operative measurements, the gradient to the adenoma side was proven by surgery, cytology and decline of cortisol postoperatively. The false lateralization was in a midline adenoma. All 10 patients with CSS had a remission. Including 3 early transnasal re-operations, among 45 patients, 98% had a remission. Multiple intra-operative cytology was performed significantly more often in children than adults.
Conclusions: Cavernous sinus sampling and cytology in difficult cases of Cushing facilitates selective transnasal microsurgery.

LB4-1525 Pituitary, Growth and Thyroid

Early over-treatment in congenital hypothyroidism is more harmful for eventual cognitive outcome than early under-treatment

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Background: The general notion is that during the treatment of congenital hypothyroidism (CHT) under-treatment (UT) should be avoided by keeping thyrotropin (TSH) concentrations in the normal reference range. Previously we showed that patients with CHT have setpoints (sp) for both free thyroxine (fT4, mean sp 22.6 pmol/l) as TSH (mean sp 3.3 mU/l), higher than in normals. FT4sp seemed more useful in guiding decisions on L-T4 dosages than TSHsp.
Objective and hypotheses: Do early OT and UT affect later cognitive outcome?

Methods: 61 Patients, 27 severe CHT, 34 mild CHT, were psychologically tested at ages 1.8, 6, and 11. The cognitive development scores were compared over time and related to initial levels of TSH normalisation (Fast, Moderate, or Slow TSHnorm) and to the total duration of UT and OT episodes during age 0-2 (No, Short, or Long UT/OT). UT and OT were defined as an fT4 concentration below/above the individual sp range (fT4sp±2SD).
Results: As compared to Slow TSHnorm, Fast and Moderate TSHnorm led to higher (14.2 and 7.7 points, respectively (p=0.001)) development scores at age 1.8, but had no significant effect on IQ11. Long and Short OT had IQ11's that were -17.8 and -13.4 points lower, respectively, than the IQ11's after No OT (p=0.014). UT without OT led to normal development scores, but UT with OT led to -14.7 points lower IQ11's than UT without OT (p=0.005).
Conclusions: Our study suggests that early OT is more harmful for CNS development than early UT. Studies from the 70's, characterized by long periods of UT, showed normal cognitive outcomes, while recent studies, performed under OT conditions, resulted in lowered IQ's. It may be that the CNS plasticity is at least partly preserved after UT, while the changes after OT seem more irreversible. The sp approach provides, especially for fT4, individual target values and ranges. The normal TSH reference range is too low. With a TSH lower limit of 0.5 mU/l up to 50% OT episodes may pass unnoticed.

LB4-1526 Pituitary, Growth and Thyroid

Monitoring of iodine deficiency in central Siberia according to the results of neonatal TSH screening

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Background: Siberia belonged to iodine-deficient regions. Our investigations showed that in Central Siberia there is a serious iodine deficiency influencing the health and mental development of the children. The program of salt iodization and iodine supplements, as potassium iodide, to high risk groups (pregnant and lacting women, children and adolescent) was started in 1996.
Objective and hypotheses: The aim of the research was to estimate the iodine deficiency and the effectiveness of IDD prevention in Central Siberia according the results of neonatal TSH- screening.
Methods: Screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency and of its control. We analyzed the neonatal TSH values of 34980 infants born in 2008-2009.
Results: According to the data of the congenital hypothyroidism screening the rate of TSH < 5 mU/1 was 11.8% in the Krasnoyarsk territory (23.9% in 2000) and corresponded to mild iodine deficiency. In different regions of the Krasnoyarsk territory the rate of TSH < 5 mU/1 in the newborn varied from 3.5% to 23.7%. The highest values were marked in the Taimyr, in Irbeysky, Suchobuzimsky, Eniseysky, Tuchtetsky, Novoselovsky regions, in Zheleznogorsk and Sosnovoborsk city (20.9- 23.7%). In Khakasia the rate of TSH < 5 mU/1 was 12.2%. In the Republic of Tyva - 6.6% (38.6% in 1997; 11.5% in 2000). It corresponding to mild iodine deficiency.
Conclusions: Our investigations show that in Central Siberia there is mild iodine deficiency demanding continuous adequate iodine prevention.

LB4-1527 Pituitary, Growth and Thyroid

Natural history of TSH receptor (TSHR) mutations gene: insights from long-term follow-up of affected children

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Background: Loss-of-function mutations in the TSH receptor gene (TSHR) lead to resistance to TSH (RTSH). Despite several reports of patients affected with TSHR mutations, data on the long-term outcome of this condition are limited and there is no consensus regarding the need for medical therapy.
Objective and hypotheses: The aim of the present study was to assess the prevalence of TSHR gene mutations and evaluate the outcome of this condition over time.
Results: Of 94 subjects (ages 3 days -21 years) that presented with non-autoimmune SCH or CH with RTSH characteristics, 27 (29%) carried mutations in TSHR gene. Eight different mutations were identified: (p.P68S); (p.Q90P); (p.P162A); (p.P264S); (p.R450C); (p.L653V); Twelve genotypes were found with rate of consanguinity (64%). Twelve subjects were homozygous, three were compound heterozygous and twelve were heterozygous. Homozygous patients had a more severe phenotype (mean TSH 45.1 vs. 9.1, p = 0.0001). Patients were followed for as long as 11 years. Mean serum TSH levels at presentation and at last visit did not differ. Five patients were identified by the neonatal screening but only one had hypothyroidism and the rest had euthyroid hyperthyrotropinemia. All the other subjects presented with non-autoimmune SCH. Subjects with one affected allele had only mild hyperthyrotropinemia with stable TSH levels. Three of the homozygous subjects have showed decreasing FT4 levels with time. Replacement therapy was initiated in 11 subjects based on laboratory results with no evidence of clinical hypothyroidism. Our results indicate that SCH in heterozygous carriers is a stable compensated condition with an appropriately adjusted set point of pituitary-thyroid feedback; however, homozygous subjects may develop uncompensated SCH that could necessitate L-T4 therapy.
Conclusions: Replacement therapy should be considered on an individual basis and long-term follow-up is recommended in subjects with TSHR mutations.

LB4-1528 Pituitary, Growth and Thyroid

Somatic mutations/rearrangements in 33 hot thyroid nodules in children

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Background: Hot thyroid nodules in children are rare. Larger pediatric cohorts have not been studied for their molecular etiology.
Objective and hypotheses: To investigate the prevalence of somatic TSHR and GNAS mutations and whether BRAF and RAS mutations, PAX8/PPARG and RET/PTC 1 and 3 rearrangements are a reason for the increased malignancy rate of hot thyroid nodules of children
Methods: DNA was extracted from formalin-fixed paraffin-embedded tissue. Real-time quantitative PCR and pyrosequencing were employed to detect TSHR, GNAS, BRAF and RAS mutations, as well as PAX8/PPARG, RET/PTC 1 and RET/PTC 3 rearrangements.
Results: 33 consecutive (29 benign and 4 malignant) hot nodules detected between 1996 and 2008 were analyzed. The age at diagnosis was 15.2 years (range 11 - 18 years). 17 of the 29 hot benign nodules (59%) harbored somatic TSHR mutations with 8 different amino acid changes. M453T mutation was the most common (8/29; 28%). The T632I and the D633Y mutation were each detected twice. All other TSHR mutations were found in 1 sample. The D727E polymorphism was detected in 9 samples: 2 homozygous and 7 heterozygous, 5 without a concomitant constitutive TSHR mutation and 4 (2 homozygous) with a concomitant TSHR mutation. GNAS mutations were not detected. A single NRAS mutation was detected in a benign hot nodule (M453T mutation). PAX/PPARG was found in 1 malignant nodule (FvPTC). T632I exchange was detected in 1 hot PTC. No other mutations or polymorphisms were identified in the 4 malignant nodules.
Conclusions: The frequency of TSHR mutations in pediatric hot nodules is within the adult range. In contrast to adults the M453T TSHR mutation is the predominant mutation. The increased malignancy rate of hot thyroid nodules of children does not appear to be associated with the analyzed neoplastic biomarkers. Novel candidate genes are still expected.

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