In normal male infants, the postnatal surge in pulsatile gonadotropin secretion is associated with a rapid expansion of Leydig and Sertoli cell populations with concomitant surges in testosterone, inhibin and AMH production. Boys with CHH are almost invariably faced with azoospermia and infertility in adult life, likely to be due to deficient FSH and proliferation of immature Sertoli cells before and during puberty. The current pilot study investigated whether the early administration of gonadotropins could mimic the physiological growth and activity of testes. Two neonates (P1) with hypothalamic and P2 isolated HH) with microopenos and micro-orchidism were treated for 6 months with high doses of recombinant LH and FSH (a gift of Luveris and Gonal-F, from SERONO) delivered subcutaneously with an insulin pump. CSIG increased serum LH and FSH levels to high normal levels. Testosterone levels reached 1-6 ng/ml in P1 and 1-4.2 ng/ml in P2. Main testicular length increased from 7-8 mm at birth to 21-25 mm at 7 months. Stretched penile length increased from 8-12 mm to 30-48 mm, respectively in P1 and P2. Serum AMH level increased to normal levels, as well as inhibin B in both infants. These results indicate that neonatal Sertoli cells do not respond to inhibition by testosterone (unlike in adults), which suggests that these cells lack androgen receptor expression, as demonstrated in neonatal mouse models. We will not know until 20-30 yrs if postnatal Sertoli cell activation favors the induction of spermatogenesis in young adults.

During the last few decades mean birth weight has increased. It is well known that maternal diabetes results in increased birth weight, but only limited information is available on mechanisms contributing to excessive fetal weight gain in non-diabetic females. The purpose was to investigate to what extent metabolic parameters were found between females and males. In males, age, weight, height, as well as to Insulin-Like Growth Factor (IGF) system. We evaluated the respective roles of HC, birth gestational age in complete weeks (GA) and caesarean section with any indication (CS) in the attainment of blood serum IGF-I (IG1) and IGF-II (IG2) in each studied NWB. IG1 and IG2 were natural logarithm-transformed (resp. ln-IG1 through chronologically corresponding ln-IG2, ln-IG1/IG2) was calculated and compared. Statistical differences between females and males. Adiponectin levels were measured by ELISA method, insulin was measured by chemiluminescent and NEFA by enzymatic colorimetric assay. Mean cord blood values in AGA subjects for adiponectin, NEFA and insulin were 26.49± 11.56µg/ml, 0.10± 1.15µg/ml and 11.56± 1.15µg/ml, respectively. No significant differences for metabolic parameters were found between females and males. In AGA subjects insulin concentrations were negatively related to gestational age (r= -0.25, p=0.05) while NEFA were negatively associated with birth weight SDS in females (r=-0.39, p=0.03). Our preliminary data demonstrate that cord blood NEFA differences between sexes should be considered in the evaluation of intrauterine growth retardation.

Low birth weight is associated with an increased incidence of visceral obesity and metabolic disorders in later life. Moreover, adipose tissue has a key role in the control of energy balance and metabolism as well as in insulin resistance, inflammation and type 2 diabetes. In the present study, we have determined the impact of birth weight and gender on metabolic markers such as insulin, non-esterified fatty acids (NEFA) and adiponectin levels in cord blood. After informed consent, 71 cord blood samples from newborns (36F, 35M) were collected and analyzed for insulin, adiponectin and NEFA. Anthropometric measurements at birth show: 5 SGA for weight and/or length (7.04%), 3 large for gestational age (4.23%) and 63 appropriate for gestational age (88.73%). Mean birth weight in AGA was 3200±429 g, mean length 50.19±1.84 cm, mean gestational age was 38.95± 1.41 weeks with no statistical differences between females and males. Adiponectin levels were measured by ELISA method, insulin was measured by chemiluminescence and NEFA by enzymatic colorimetric assay. Mean cord blood values in AGA subjects for adiponectin, NEFA and insulin were 26.49± 11.56µg/ml, 0.10± 1.15µg/ml and 11.56± 1.15µg/ml, respectively. No significant differences for metabolic parameters were found between females and males. In AGA subjects insulin concentrations were negatively related to gestational age (r= -0.25, p=0.05) while NEFA were negatively associated with birth weight SDS in females (r=-0.39, p=0.03). Our preliminary data demonstrate that cord blood NEFA differences between sexes should be considered in the evaluation of intrauterine growth retardation.

Birth head circumference (HC) has been related to postnatal derangements as well as to Insulin-Like Growth Factor (IGF) system. We evaluated the respective roles of HC, birth gestational age in complete weeks (GA) and caesarean section with any indication (CS) in the attainment of blood serum IGF-I (IG1) levels and of ratios between IG1 and blood serum IGF-II (IG2) in a human newborn (NWB) sample. The 78 NWBs included in the study showed the following characteristics: gender (SEX), male, sex, SE =43; GA range=28-42; GA<36, n=46; birth body weight <10th centile for GA (SGA), n=20; CS, n= 52; malformedive syndrome and/or postnatal systemic corticosteroid treatment, n=0; life-threatening disease and/or diabetes mellitus (DM), n=0; mother with DM, n=0. IG1 and IG2 were measured by Radioimmunoassay in picomoles/deciliter at one of the first 5 postnatal days (x), 5 days after x (y) and 10 days after x (z) in each studied NWB. IG1 and IG2 were natural logarithm-transformed (resp. ln-IG1 and ln-IG2) and a ln-IG1/ln-IG2 ratio (ln-IG1 through chronologically corresponding ln-IG2, ln-IG1/IG2) was cal-
calculated. ln-IG1 and ln-IG1/IG2 resulted near-normally distributed. Table 1 showed R2/F of Multiple Linear Regression Analysis (MRA) models including different models of ln-IG1 and ln-IG1/IG2 as outcome variable and either a) HC, SEX, CS and SGA (Table 1/A), or b) HC, SEX, CS, SGA and GA (Table 1/B) as predictors (computations; male SEX, CS, SGA, condition present=1, condition absent=0), 2) t/r values of partial correlations between predictor and outcome variable for each MRA model and 3) significances of MRA models and their partial correlations.

HC resulted significantly associated in direct way with ln-IG1 and ln-IG1/IG2 and transient hypothyroidism of 1:6988 (2003) to 1:15593 (2004). The last was observed in the neonatal period i.e.: hyperthyrotropinemie and 0.01% in years 2006-2007. Conclusion: The decrease of percentage of cy disorders (IDD) incidence in neonatal screening and IDD incidence, observed in the years in southeastern Poland.

### Table 1

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HC resulted significantly associated in direct way with ln-IG1 and ln-IG1/IG2 and transient hypothyroidism of 1:6988 (2003) to 1:15593 (2004). The last was observed in the neonatal period i.e.: hyperthyrotropinemie and 0.01% in years 2006-2007. Conclusion: The decrease of percentage of cy disorders (IDD) incidence in neonatal screening and IDD incidence, observed in the years in southeastern Poland.

### P2-d2-512 Perinatal Endocrinology

**Normal variations in maternal plasma glucose and insulin levels during pregnancy are closely related to offspring body composition**

**Barbro Diderholm**<sup>1</sup>; Ken K Ong<sup>2</sup>; Leuan A Hughes<sup>3</sup>; Carlo L Acerini<sup>4</sup>; David B Dunger<sup>5</sup>

<sup>1</sup>University of Cambridge, Department of Paediatrics, Cambridge, United Kingdom; <sup>2</sup>Medical Research Council, Epidemiology Unit, Cambridge, United Kingdom

Increased glucose delivery is one mechanism underlying offspring macrosomia in gestational diabetes. This study investigated perinatal influences of more common variations in maternal glucose and insulin levels on birth outcomes, offspring birth weight and postnatal weight gain. Two population-based birth cohorts, one retrospective (n=3,158) and one prospective (n=668) were studied. Glucose tolerance was assessed at 28 weeks gestation by oral glucose load. Stimulated glucose levels within the normal range in both cohorts and fasting insulin sensitivity in the second cohort were related to various birth outcomes. In the retrospective study, each 1 mmol/L rise in maternal 60 min stimulated glucose level was associated with reduced birth weight (β=-0.16; p=0.002). The birth weight effect was independent of maternal BMI and birth weight at birth. In the prospective study, maternal fasting, rather than stimulated, glucose level had the strongest effect on offspring skinfold thickness at birth (p<0.004). Independent of maternal glucose levels, additional effects of maternal insulin sensitivity (R=-0.129, p=0.01) and insulin secretion (R=-0.137, p=0.02) were observed on skinfold thickness at birth. Independent of maternal glucose levels, maternal BMI correlated both with body weight and length at birth (p<0.05); associations between maternal BMI and offspring skinfold thickness developed from postnatal ages 12 to 24 months (p<0.05). In conclusion, maternal glycaemia is related to birth size, body composition and birth outcomes continuously in the non-diabetic range. Further associations with maternal insulin sensitivity may reflect the additional influences of maternal non-glucose metabolites on fetal growth. Finally, the independent associations between maternal glycaemia, maternal BMI, size at birth and postnatal growth may reflect distinct fetal and postnatal nutritional effects on fetal and postnatal growth.

### P2-d2-513 Perinatal Endocrinology

**Head circumference at birth as a predictor of relationship between circulating levels of insulin-like growth factor I and insulin-like growth factor binding proteins 2 and 3 in newborns who are not life-threatened: Role of caesarean section and of gestational age**

**Cesare Terzi**<sup>1</sup>; Werner F Blum<sup>2</sup>; Rafaele Virdis<sup>3</sup>; Cristiana Magnani<sup>4</sup>; Sergio Zani<sup>5</sup>; Marco Riani<sup>6</sup>; Franco Rossi<sup>7</sup>; Andrea Cerioli<sup>1</sup>; Lidia Garavelli<sup>1</sup>; Sergio Bernasconi<sup>1</sup>; Giorgio Giovannelli<sup>1</sup>; Giacomo Banchini<sup>1</sup>

<sup>1</sup>University of Parma, Dept.of Pediatrics, Parma, Italy; <sup>2</sup>University of Giessen, Dept.of Pediatrics, Giessen, Germany; <sup>3</sup>ospedale S. Maria Nuova Reggio Emilia, Pediatrics, Reggio Emilia, Italy; <sup>4</sup>University of Pavia, Dept.of Economics, Pavia, Italy; <sup>5</sup>Medical School, S. Maria Nuova, Dept.of Obstetrics and Gynecology, Reggio Emilia, Italy; <sup>6</sup>ospedale S. Maria Nuova Reggio Emilia, Dept.of Pediatrics, Parma, Italy; <sup>7</sup>ospedale S. Maria Nuova Reggio Emilia, Dept.of Pediatrics, Reggio Emilia, Italy

Birth head circumference (HC), a long-term risk determinant, birth gestational age in complete weeks (GA) and caesarean section with any indication (CS) were evaluated as predictors of relations between blood serum levels of Insulin-Like Growth Factor (IGF) I (IG1), and of IGF binding proteins 2 and 3 (resp IB2 and IB3) in the human newborn (NWBD). The 78 NWBDs included in the study showed the following characteristics: gender (SEX), male SEX, n=43, GA range=28-42, GA≤36, n=46; birth body weight <10.th centile for GA
an international collaborative report on 15 new mutations

Pascal Philibert1; François Audrain2; Catherine Pienkowski3; Birgit Koeler4; Isabelle Morange5; G Ogür6; C Dacou7; S Ten7; Françoise Paris8; Charles Sutcliffe9; CHU, Hormonologie, Montpellier, France; CHU, Endocrinologie Pédiatrique, Montpellier, France; CHU, Endocrinologie Pédiatrique, Toulouse, France; CH, Pédiatrie, Berlin, Germany; CH, Pédiatrie, Marseille, France; CH, Pédiatrie, Ankara, Turkey; CH, Pédiatrie, Athens, Greece; CH, Pédiatrie, New York, United States

Complete androgen insensitivity syndrome (CAIS) is defined by the association of an unambiguous female phenotype and the absence of uterus in 46,XY patients with normal tests differentiation and high androgen production. It results from mutations in the androgen receptor (AR) gene. According to the International Mutation Database, more than 250 different mutations can give results from mutations in the androgen receptor (AR) gene. According to the

HC resulted significantly related in direct way to ln-IG1/IB2 and to ln-IG1/IB3 and in inverse way to ln-IB2/IB3 in not life-threatened NWBs, after control for CS, SEX and SGA, through mechanisms likely involving GA.

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<td>Central diabetes insipitus in Pallister-Hall syndrome: First case report</td>
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<tr>
<td>Hakan Donenay1; Ya-Gang Xie2; Ayhan Tastekin3; Zerrin Orbak4</td>
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</table>
1 Atatürk University Faculty of Medicine, Department of Pediatric Endocrinology, Erzurum, Turkey; 2 Memorial University Faculty of Medicine, Discipline of Laboratory Medicine, Newfoundland, Canada; 3 Atatürk University Faculty of Medicine, Department of Neonatology, Erzurum, Turkey |

Pallister-Hall syndrome (PHS) is an autosomal-dominant malformation syndrome. It has been shown to be caused by mutations in GLI3 gene. PHS is characterized by hypothalamic hamartoma, polydactyly, dysplastic nails, bifid epiglottis, and imperforate anus. PHS may have endocrine abnormalities including panhypopituitarism, isolated growth hormone deficiency, and precocious puberty. However, PHS associated with central diabetes insipitus has not been reported in the literature. We present a first case of PHS associated with central diabetes insipitus. A 3-day-old male neonate was referred our clinic because of dismorphic findings in examination and seizures. He was born at term after an unremarkable pregnancy and the second child of non-consanguineous parents. His birth weight, length and head circumference were below 10th centile. Facially, there was frontal bossing, a short nose with flat nasal bridge, and antverted nares. The corners of mouth were down turned. Both hand had heptactadactyly characterized by insertional and postaxial polydactyly. Brachydactyly and nail hypoplasia affecting all digits were noted. The patient developed generalized seizures at 3 days of age and a magnetic resonance imaging (MRI) scan was undertaken, which revealed holoprosencephaly, hypoplasia of corpus callosum and hydrocephalia. Seizures were controlled with the anticonvulsants. Hypernatremia (155 mmol/L) was determined at 10 days of age. Serum and urine osmolalities were 345 and 150 mOsm/kg, respectively, TSH, T4 and FT4 levels at the time were 4.4 uU/mL, 5 mcg/dL, and 0.2 ng/dL, respectively. The evaluation of other hypophysal hormones was normal. Serum and urine osmolalities and thyroid function tests were normalized after desmopressin and Na-L-thyroxin therapy, respectively. Urinary ultrasonography was normal. Echocardiography showed atrial septal defect. Genetic analysis identified a mutation in the GLI3 gene. In conclusion, central diabetes insipitus can be accompanied by PHS. Therefore, we consider that serum osmolality in patients with PHS should be controlled.

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<th>Table 1</th>
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<td>vs. IG1/IB2x</td>
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<td>r/t</td>
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<tr>
<td>vs. IG1/IB3x</td>
<td>IG3/IB3y</td>
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**P2-d2-515 Sex Differentiation**

Premature stop codon within exon 1 of the androgen receptor gene is a frequent cause of complete androgen insensitivity syndrome: an international collaborative report on 15 new mutations

Pascal Philibert1; François Audrain2; Catherine Pienkowski3; Birgit Koeler4; Isabelle Morange5; G Ogür6; C Dacou7; S Ten7; Françoise Paris8; Charles Sutcliffe9; CHU, Hormonologie, Montpellier, France; CHU, Endocrinologie Pédiatrique, Montpellier, France; CHU, Endocrinologie Pédiatrique, Toulouse, France; CH, Pédiatrie, Berlin, Germany; CH, Pédiatrie, Marseille, France; CH, Pédiatrie, Ankara, Turkey; CH, Pédiatrie, Athens, Greece; CH, Pédiatrie, New York, United States

Complete androgen insensitivity syndrome (CAIS) is defined by the association of an unambiguous female phenotype and the absence of uterus in 46,XY patients with normal tests differentiation and high androgen production. It results from mutations in the androgen receptor (AR) gene. According to the International Mutation Database, more than 250 different mutations can give rise to CAIS, but a small number are located in the N-terminal domain of the AR encoded by exon 1, a region of the AR gene difficult to sequence. In the last 10 years, we have identified 78 AR gene mutations among 165 patients with CAIS. Twenty-one of them were located within exon 1. The aim of this work was to determine whether exon 1 AR gene mutation is a frequent cause of AR transactivation defect in patients with CAIS. The 15 new AR gene mutations are reported on the figure:
In all cases, a nucleotide substitution leading to a stop codon was observed. By inducing the formation of a truncated protein, it is likely that AR transactivation activity is abolished in these patients with CAIS. These data show that exon 1 AR gene mutation is a frequent cause of CAIS (21/78), conversely to the claims of some investigators.

In the literature, exon 1 AR mutations (n=36) represent about 15% of all AR gene mutations reported in patients with CAIS. In our experience, the high frequency (27%) of premature stop codons with exon 1 of the AR gene justifies the sequencing of exon 1 in patients with CAIS.

**P2-d2-516 Sex Differentiation**

**Towards analysis of the molecular etiology of gonadal differentiation in patients with disorders of sexual development and a Y chromosome in the karyotype (DSD-Y)**

Sabine Knauer-Fischer; Banu Güler; U. Bender; Ioana Inta; Daniela Klose; Peter H. Vogt; Markus Bettendorf

1 University Children’s Hospital, Dept. of Pediatric Endocrinology, Heidelberg, Germany; 2 Women Hospital, University of Heidelberg, Dept. Gynecol, Endocrinol. & Reprod. Medicine, Heidelberg, Germany

Genomic mapping studies in females with dysgenetic gonads and with a Y chromosome in their karyotype (DSD-Y group) have revealed that Y genes in proximal Yp and Yq are probably involved in the 30% risk for gonadal development (Gonadoblastoma Y locus; GBY). We want to reveal any dysfunction of these GBY candidate genes in the DSD-Y patients. For this purpose we have established a detailed clinical questionnaire and sensitive Y gene deletion PCR assays in the GBY region and the flanking azoospermia factor (AZF) regions, AZFb, AZFc, known to be functionally important in the male germ line. Our database currently includes 25 idiopathic DSD-Y patients. Karyotype analyses distinguished 10 individuals with a 46,XY constitution, 11 individuals with a mosaic 45,X0/46,XY, 2 individuals with X;Y translocation and 2 individuals with a 45,XY marker constitution. Each group comprises heterogeneous patients concerning gonads, genitalia and the presence or absence of Mullerian structures. No interstitial Y gene deletion was found in Yq11, but terminal deletions including deletion of numerous Y genes were found in 12 DSD-Y individuals with two prominent breakpoint regions distal to the GBY region. Individuals with a Y marker constitution displayed deletion of all Y genes including those in the GBY region. We conclude that the DSD-Y patient group is very heterogeneous concerning gonads, internal and external genitalia and that their 30% tumor risk is heterogeneous as well. Patients with only a Y marker but no Y genes have probably only a low tumor risk. Most interestingly, DSD-Y patients had a female or male phenotype only when the long Y arm was broken proximal to the AZFb region, i.e., including only the GBY candidate genes on their Y chromosome. DSD-XY patients with Yq11 breakpoints in AZFb or distal of it had always a male phenotype.

**P2-d2-517 Sex Differentiation**

**An XX male with an intratubular undifferentiated germ cell neoplasia**

Aitiano Caravella; Milagros Alonso; Raquel Barrio; Purificacion Ros; Begoria Ezquieita; Eva Garcia-Galloway; Manuel Nistal

1 Ramón y Cajal Hospital, Pediatrics Department, Madrid, Spain; 2 Gregorio Marañón Hospital, Molecular Diagnostics Unit, Madrid, Spain; 3 Ramón y Cajal Hospital, Genetics Department, Madrid, Spain; 4 La Paz Hospital, Department of Pathology, Madrid, Spain

The risk for the development of germ cell tumors is an important factor to deal with in the management of patients with disorders of sex development. The recent consensus of intersex disorders offer recommendations for management in these cases. It is suggested that this model should be tested after examination of well characterized patients. We report a case of a 46XX male with an intratubular undifferentiated germ cell neoplasia IUGCN within an extrabdominal gonad. The child was followed in our Pediatric Endocrine setting for ambiguous genitalia with descended testes at birth. Bilateral testicular biopsies were performed at the age of 5 months, showing dysgenetic testes. The child was raised as a boy and underwent several surgical interventions to perform the correction of his genitalia. By the age of 15 hormonal investigation revealed hypergonadotropic hypogonadism, so he started on testosterone treatment. When he was 17 a spermogram revealed azoospermia. The patient had a normal length penis and desired testicular prostheses. By the age of 18 the decision was taken, all together with the family and the medical staff, to proceed to bilateral orchiecetomy and insertion of testicular prostheses. We perform conventional chromosome analysis revealing a 46Xq- karyotype. FISH experiments with the SRY probe found a signal at the short arm of the deleted X chromosome. Molecular analysis indicated the presence of a portion of the short arm of the Y chromosome including the protooncogene TSPY. Pathologic evaluation of the gonads with immunostaining for placental alkaline phosphatase and C-kit revealed an IUGCN. This is the first case of a 46,XX male with desended dysgenetic testes who developed an IUGCN. It must be taken into account to formulate proposals of management in this sub-group of disorders of sexual differentiation, according to the risk of germ cell malignancy.

**P2-d2-518 Sex Differentiation**

**46XY DSD with PAIS due to novel androgen receptor (AR) mutation (G577E) with Müllerian Ducts remnants**

Brigitte Mignot; Anne-Marie Bertrand; Claire Ballot; Muriel Francois; Didier Aubert; Nathalie Jossot; Claire Fekete; Yves Morel

1 CHU Besançon, Endocrinologie Pédiatrique, Besançon, France; 2 CHU Besançon, Chirurgie Pédiatrique, Besançon, France; 3 Inserm 782, Endocrinologie et Genetique de la Reproduction et, CIMAR, France; 4 Hopital Necker, Chirurgie Pédiatrique, Paris, France; 5 CBPE, Endocrinologie Moléculaire et Maladies Rares, Bron- Lyon, France

Case Report: The patient was born full term with DSD: penile length of 18 mm, perineal hypopasidias, inguinal gonads of normal size. Maternal familial history (South American) was revealed to the mother after this birth only, with three other affected members (all assigned in men) including her own brother. These men had posterior hypopasidias with surgical procedures, gynecostasia, sterility, small penile size with inefficient testosterone treatment. All these male members have profound psychological and sexual difficulties. Our patient had 46 XY Karyotype. Testosterone was normal at birth (3.1 nmol/l), elevated 19 days after birth (17.3 nmol/l) with high basal LH levels (8.6 UI/l). AR gene was sequenced and showed a novel mutation on p.G577E in exon 2. Another mutation (p.G577R) affecting same aminoacid has already been described but unfortunately without providing published information about long term follow-up. These mutations result in selective decreases in DNA binding and in PAIS. Moreover, in our patient, genitoidnoscope revealed uterus with two fallopian tubes. Considering these findings with normal high levels of AMH (465 pmol/l), we sequenced AMH receptor (AMHR) gene but no mutation was found. Gonadectomy and feminizing genitoplasty were performed. Female sex was assigned. The poor evolution of the three affected boys was a crucial point in gender assignment.

Discussion: This case report is interesting on different points of view: -> The familial history was initially unknown while the own brother mother was affected. That was a key point in assignment of gender. This highlights the
strong necessity to look for the precise familial history (sometimes hidden).

- Mullerian structures in AIS have already been reported. Some mechanisms for absence of Mullerian Ducts regression in AR mutation have been suggested as AMHR mutation, unavailable hypothesis in our patient. Further studies should promote a better understanding of this pathogenic association.

P2-d2-519 Sex Differentiation
The IVS1-2A>G mutation in the SRD5A2 gene is present in all Greek Cypriot patients with 5 alpha reductase deficiency diagnosed so far
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5 Alpha Reductase deficiency (5a SRD) is caused by mutations in the 5a Steroid Reductase type 2 gene (SRD5A2). More than 40 gene mutations have been reported worldwide, with some recurrent mutations commonly reported among various ethnic populations while other mutations reflect a founder gene effect in individuals with a common ancestry. The aim of our study was to identify the genetic defect in the SRD5A2 gene in Greek Cypriot patients with 5a SRD, whose diagnosis was based on clinical and biochemical criteria. Four unrelated patients with 46, XY karyotype and 5a SRD were investigated. Patients 1, 2 and 3 presented with ambiguous genitalia at birth whereas patient 4 (raised as girl) presented at the age of 14 years with signs of sexual infantilism and virilization. The HCG test was informative of 5a SRD, as showed an elevated T/DHT ratio (23.5, 29 and 29.6) after stimulation. All five exons of the SRD5A2 gene were screened for mutations by direct sequencing of PCR products. Patients 1, 3 and 4 were found homozygous for the mutation A>G at the splice site of intron 1/exon 2 (IVS1-2A>G/IVS1-2A>G). Patient 2 was compound heterozygote for the mutations IVS1-2A>G and Pro181Leu. The same mutation (IVS1-2A>G) in the SRD5A2 gene was identified in four unrelated patients, both in homozygous and heterozygous state. This splice site mutation seems to characterize our population and is probably due to a gene founder effect. This underlying genetic abnormality has been already reported in Turkish patients and it may be characteristic for the Eastern Mediterranean region. The Pro181Leu mutation found most probably does not reflect a founder effect as it has been previously identified in patients of Italian origin.

P2-d2-520 Sex Differentiation
Three new mutations in androgen receptor gene identified in patients with 46,XY SDS: Complications for genetic counselling
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Androgen receptor insensitivity syndrome (AIS) is characterized by a wide spectrum of phenotypes ranging from 46,XY subjects with complete female to normal male with infertility, more then 500 mutations are reported in the AR gene, mostly inherited in X-linked manner, few cases presented de novo mutations. In these last 20 years in vitro and in vivo functional studies on mutated androgen receptor, the determination of 3D structure of hormone binding domain, the identification of wide number of cofactors interacting with the androgen receptor, and the more recent studies of expression of genital tissue, gave a big contribute to understand the bio-molecular and pathogenetic aspects of androgen action. Here we reported the results of the analysis of AR gene in four patients with AIS, that we consider emblematic of how all these acquisitions on androgen receptor biology could help the clinical correlation of new mutations, but also highlight some critical aspects regarding in particular the genetic counselling to the families. All the patients has 46,XY karyotype, two are sisters with complete female genitalia, diagnosed for the presence of inguinal hernia in the older sister, the other two are males with a severe hypospadias. The genomic DNA was isolated from peripheral blood

P2-d2-521 Sex Differentiation
Phalloplasty as a treatment for severe penile insufficiency
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Males with severe penile insufficiency in conditions such as penile agenesis, microphallus or some disorders of sex development (DSD) remain a major challenge to the reconstructive urologist. With a large experience using phalloplasty in female-to-male transsexual surgery, we started to use this technique for severe penile insufficiency. Eleven males (age 15 to 42 years) were treated with phalloplasty (7 with radial forearm free flap and 4 with anterolateral thigh flap) between March 2004 and December 2007 (follow-up: 3 to 47 months). All patients suffered psychologically from their condition with a low self-esteem and sexual and relational dysfunction. They were evaluated by a sexologist-psychotherapist before and after surgery. Erectile implant surgery was offered about one year after the phallic reconstruction. There were no complications concerning the flap. Two complications (pulmonary embolism and severe hematuria) were reported in the early post-operative period. Four patients developed urinary complications (stricture and/or fistula). Patient satisfaction after surgery was high in 10 cases and moderate in one case. Psychological evaluation confirms this, especially on the self-esteem level. Six patients underwent erectile implant surgery. In 2 patients the erectile implant had to be removed due to infection or erosion. Our first experience with phalloplasty in young males has convinced us that this technique is a valuable treatment for severe penile insufficiency. It has good results on the self-esteem level and their sexual well-being. However, urinary complications occurred in 4/11 patients and explantation of the erectile implant occurred in 2/6 patients. Patients must be informed about these possible and frequent urological complications. This technique opens new horizons for the treatment of conditions such as penile agenesis, microphallics, some DSD conditions and cloacal exstrophy. More research is necessary on the criteria for patient selection, prevention of complications, and long-term functional and psychological outcome.

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Patient | Indications | Type of phalloplasty | Age (years) | Follow-up (months) | Penile prosthesis
--- | --- | --- | --- | --- | ---
1 | Shrivelled penis - infected penis stiffener | Anterolateral thigh flap | 42 | 38 | AMS Ambicor, 2 cylinders
2 | Shrivelled penis - bladder exopythry | Radial forearm free flap | 23 | 47 | AMS Ambicor, 2 cylinders
3 | Shrivelled penis - bladder exopythry | Radial forearm free flap | 16 | 40 | AMS Ambicor, 2 cylinders
4 | Penile amputation - epitheloid sarcoma | Radial forearm free flap | 15 | 24 | No
5 | Crippled penis - hypospadias | Radial forearm free flap | 20 | 24 | No
6 | Shrivelled penis - bladder exopythry | Radial forearm free flap | 15 | 22 | No
7 | Penile necrosis - traffic accident | Radial forearm free flap | 32 | 37 | AMS Ambicor, 2 cylinders
8 | Cloacal exstrophy | Anterolateral thigh flap | 16 | 8 | No
9 | Cloacal exstrophy | Anterolateral thigh flap | 16 | 8 | No
10 | Micropenis - partial androgen insensitivity syndrome | Radial forearm free flap | 30 | 13 | No
11 | Penile necrosis - priapism | Anterolateral thigh flap | 38 | 3 | No
Background: Patients with Ullrich-Turner syndrome with a Y-chromosomal genotype were assigned to female and children with DSD, especially when the diagnosis is delayed.

Introduction: Disorders of sexual differentiation (DSD) are a distressing problem for the family especially when they pose the problem of gender assignment. Our retrospective study highlights the difficulties in managing children with DSD, especially when the diagnosis is delayed.

Methods: We describe 97 cases of children who presented with DSD and who were followed between 1994 and 2007. We excluded 50 cases of isolated microopenis, 2 cases of fused labia minora, and 2 cases where the penis was buried in adipose tissue. Diagnosis was made on the basis of clinical, hormonal, and radiological assessment; molecular genetic analysis was carried out in some patients.

Results: Congenital adrenal hyperplasia (CAH) is a common autosomal recessive disorder that is mostly caused by 21-hydroxylase deficiency (21-OHD) due to defects in the CYP21A2 gene. Congenital adrenal hyperplasia(CAH) is a common autosomal recessive disorder that is mostly caused by 21-hydroxylase deficiency (21-OHD) due to defects in the CYP21A2 gene.

Objective: To review the clinical and laboratory features and follow up of patients with 45 XO/46 XY genotype.

Methods: Ten patients followed for mixed gonadal dysgenesis since 1983 were reviewed retrospectively.

Results: The age at the presentation was between 4 days to 15 years. Height SD score of patients were between -5.69 and 0. The presenting symptoms were ambiguous genitalia, short stature, abnormal penile shape. At the initial presentation general appearance of external genitalia was ambiguous in 8 cases. Turner syndrome was present in 2 cases. Eight cases had at least one palpable gonad, remaining 2 patients had no palpable gonad. Congenital anomaly was described on peripheral blood leucocytes showed 45XO/46XY in 8 cases 45XO/46X+marY in one case and 45XO/46X,idi(Yq)1 47X,idi(Yq)x2/47XYY in one case. Investigation of internal genitalia revealed Mullerian derivatives in all cases and additional Wolfian structures in 2. Histological examination of gonads demonstrated tests on one side and streak gonad on the contralateral side in 7 cases. Gonadal functions were evaluated with basal and/or human chorionic gonadotropin (hCG) stimulated testosterone levels.

Conclusion: In the cases with early presentation at infancy gender assignment was based on basal or hCG stimulated testosterone levels. However, cases with late presentation were left in the gender they were reared.
Results: Disease-causing mutations were identified in 91 out of 106 alleles (85.8%) of the patients. The most frequent mutations were IVS-2-13C-G (22.6%), p.R356W (9.4%), p.I172N (9.4%) and del (7.5%). In the SW form, the most frequent mutation was IVS-2-13C-G (22.2%), followed by conv (20.4%), p.R356W (12.9%), del (11.1%), and the p.Q318X (9.2%) mutation. In one of the SW patients a heterozygous deletion of the CYBPE region was observed, and in the other two patients a homozygous deletion of the CYBPE region was found. In one of the SW patients a heterozygous deletion of the CYBPE region was observed, and in the other two patients a homozygous deletion of the CYBPE region was found.

In the second month of life, the patient was referred for endocrinologic evaluation because of abnormal external genitalia with labiospadias and undescended testes. Physical examination revealed that the patient had bilateral testes in the inguinal canal and a small penis. A karyotype of 46,XY was performed. The patient was then referred to the Department of Pediatric Endocrinology for further evaluation.

The patient was found to have a deletion of the AZF region of the Y chromosome. A deletion was also detected on the AZF region of the Y chromosome.

Conclusions: This is the first comprehensive study on the molecular basis of CAH patients in Turkish population. Based on these results, we propose a modified screening strategy to facilitate molecular testing.
P2-d2-529 Sex Differentiation

Final adult height, pubertal development, surgical outcome, sexual function and fecundity rates in Egyptian patients treated for 21-hydroxylase deficiency

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Background: Congenital adrenal hyperplasia (CAH) is commonly misdiagnosed in Egypt due to absence of neonatal screening and lack of physician awareness of the disease.

Aim: To evaluate, in a retrospective study, final adult height (FH), pubertal patterns, surgical outcome, sexual function and fecundity in CAH. Patients: 28 patients (23 females & 5 males) affected by 21-hydroxylase deficiency were classified into 3 groups according to clinical criteria: salt-wasting (SW), simple virilizing (SV) and nonclassical (NC) forms.

Results: FH was lower in the classic groups (SV & SW) than the NC form. The most significant loss of FH occurred in SV males. Early diagnosis, lower cortisol doses and addition of mineralocorticoid therapy improve FH. In the classic group, the onset of puberty was early, 6.8 yr for girls & 7.0 yr for boys. 8 patients developed pseudoprecocious puberty with a markedly advanced bone age, hence they received LHRH analogues. Age at menarche occurred about 2.5 yr later in SW females than in the other 2 groups. For females, 18 underwent feminizing genioplasty in childhood, 3 were reared as males as they were diagnosed late at 6, 7 & 18 yrs. Normal clitoral anatomy was noticed in 14 females, abnormal clitoral sensation in 3 & painful sexual arousal in 2. Inadequate vaginas & penetration difficulties were found in 14 girls. For female CAH reared as females, gender identity was clearly female. However, less satisfaction with sexual function was noticed in those treated late. Polycystic ovarian syndrome is reported in 50% of females. Ten SV females attempted fertility, 2 had successful induced conception. For NC patients, 6 attempted fertility & succeeded (3 spontaneous and 3 induced).

Conclusion: Early diagnosis, use of more physiological cortisol doses & mineralocorticoid therapy for all classical patients improve FH. Poor surgical outcome was noticed for feminizing genioplasty performed during childhood. Psychological adjustment does not appear to be compromised in CAH females. Fecundity rate is better in NC females than SV form.

P2-d2-530 SGA

First year growth response to GH therapy in short prepubertal SGA patients: Results from standard clinical practice in Belgium

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Persisting short stature after a SGA birth has become an important indication for GH therapy in Belgium since 2004. Clinical trials (CT) have shown a GH dose and age dependent height increase during the 1st year of therapy. A prediction model for the 1st year height velocity (HV) during GH therapy, based on responses of the patients in a pharmacovigilance study (KIGS), has been published. To guide the therapeutic approach of short SGA patients. We compared the 1st year growth response observed in standard clinical care with the results of published CT’s and the KIGS model. From the 222 SGA children in the Belgian Growth Registry, we selected all who remained prepubertal and had a height measurement after > 0.7 and < 1.4 yr of GH administration. In 89 (51 boys) SGA children GH was started with a median (range) dose of 0.26(0.13 - 0.64) mg/kg/week at a median age of 8 yr (4-15). 68 (78 %) children had a height velocity (HV) above +1SD after one year of GH therapy. Mean (sd) height SDS increased significantly from -2.5(0.7) to -2.0(0.8), and the response was similar in girls and boys and irrespective of the cause of the intra-uterine growth retardation. The change in height SDS correlated negatively with age (r = -0.34; p=0.001) and positively with the GH dose (r = 0.24;p=0.024). First year mean (sd) HV (cm/yr) was 8.2(1.5), which was comparable to the predicted HV of 8.2(0.8). The difference between observed and predicted HV (mean(SEM): 0.03(0.15) increased with height SDS (r =0.30;p=0.007) and HV (r=0.84, p<0.0001). The magnitude and age and dose dependency of the growth response to GH was confirmed in SGA patients with a wider age range than previously studied. The KIGS model was found to predict the 1st year growth HV within confidence limits of 2 cm, but with some degree of overfitting.

P2-d2-531 SGA

The influence of prematurity on body composition before and during growth hormone (GH) treatment in short small for gestational age (SGA) children

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Background: GH treatment of short SGA children results in a decrease in fat percentage while lean body mass corrected for height remains at a similar level. It is unknown whether preterm birth has an independent influence on the change in body composition during GH treatment.

Objective: To compare preterm and term short SGA children with respect to changes in body composition during GH treatment.

Patients and methods: Body composition was measured by Dual Energy X-ray absorptiometry at baseline and after 6, 24 and 48 months of GH treatment (1 mg/m²/d) in 53 preterm (gestational age < 36 weeks) and 93 term short SGA children. All children were prepubertal.

Results: Preterm SGA children had a lower birth weight and -length SDS than term SGA children (Table 1). Preterm children were taller at start of GH but had a lower fat percentage SDS while lean mass SDS was comparable with term children. GH treatment resulted in a similar decrease in fat percentage SDS in preterm and term children and a similar increase in height SDS.
Conclusion: Preterm short SGA children have a lower fat percentage than term short SGA children. GH treatment affects lean mass corrected for height differently in preterm children than in term children.

**P2-d-532 SGA**

Fat accumulation during childhood is a risk factor for a higher adult blood pressure whereas prenatal growth is not.

**The PROGRAM/PREMS-study**

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Background: The association between birth weight and subsequent blood pressure is the most investigated association regarding the fetal origins hypothesis, but clarity is still lacking. Other mechanisms might be more relevant, like catch-up growth.

Objectives: We hypothesized that weight gain during childhood, specified as fat accumulation, is an important risk factor in subsequent blood pressure, whereas prenatal growth is not. Thereby, we hypothesized that gestational age has an inverse association with subsequent blood pressure.

Methods: In the extended PROGRAM-study, a cohort of 293 subjects, aged 18-24, blood pressure was measured by 13 consecutive measurements to reflect 24-hours blood pressure. By multiple regression (MR) analyses, the relationship between birth size and catch-up growth and subsequent blood pressure was determined. In addition, differences in blood pressure were analyzed in 5 clinically relevant subgroups, young adults either born Small for Gestational Age with short stature or with catch-up growth (SGA-CU) or, born Appropriate for Gestational Age with Idiopathic Short Stature or with catch-up growth (AGA). Twenty six SGA SGA wCU; children of mean age of 7.0 years, height SDS -0.88; 26 SGA nCU; mean age of 6.1 years, height SDS -2.27; and 48 AGA pubertal children, mean age of 7.2 years, height SDS -0.16 were examined. Adiponectin, proinsulin, leptin, IGF-I, IGFBP-1, GHBP, insulin, HOMA-IR, and HOMA-B were determined. Analysis of variance and Spearman correlation were used. SGA children of both sexes had similar adiponectin values; AGA girls had higher adiponectin values (p=0.03). Leptin values were higher in children born SGA cg (p=0.05) and the correlation with insulin sensitivity parameters was similar to that of AGA children. Leptin showed differences relative to sex in the three groups analyzed. Our study shows that prepubertal children born SGA have adiponectin levels comparable to those of control children, independently of catch-up growth. Higher leptin levels in SGA cg group and its correlation with insulin sensitivity parameters suggest a leptin resistance as an adaptive mechanism to increase their energy balance; however, an altered functional response of adipocytokines secondary to foetal malnutrition cannot be discarded.

**P2-d-533 SGA**

Serum levels of adiponectin and leptin in children born small for gestational age relative to insulin sensitivity parameters and growth factors

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Children born small for gestational age (SGA) are more prone to developing obesity, insulin resistance, type 2 diabetes, and cardiovascular disease. Adiponectin and leptin are fat cell-derived proteins and have been associated with insulin sensitivity. The physiological role of these adipocytokines is yet to be completely determined. To relate adiponectin and leptin levels with insulin sensitivity parameters we compared children born SGA with and without catch-up growth (SGA wCG; SGA nCG ) with a control group of healthy children who were appropriate for gestational age (AGA). Twenty three SGA SGA wCG; children of mean age of 7.0 years, height SDS -0.88; 26 SGA nCG; mean age of 6.1 years, height SDS -2.27; and 48 AGA prepubertal children, mean age of 7.2 years, height SDS -0.16 were examined. Adiponectin, proinsulin, leptin, IGF-I, IGFBP-1, GHBP, insulin, HOMA-IR, and HOMA-B were determined. Analysis of variance and Spearman correlation were used. SGA children of both sexes had similar adiponectin values; AGA girls had higher adiponectin values (p=0.03). Leptin values were higher in children born SGA cg (p=0.05) and the correlation with insulin sensitivity parameters was similar to that of AGA children. Leptin showed differences relative to sex in the three groups analyzed. Our study shows that prepubertal children born SGA have adiponectin levels comparable to those of control children, independently of catch-up growth. Higher leptin levels in SGA cg group and its correlation with insulin sensitivity parameters suggest a leptin resistance as an adaptive mechanism to increase their energy balance; however, an altered functional response of adipocytokines secondary to foetal malnutrition cannot be discarded.

**P2-d-534 SGA**

Carotid artery intima-media thickness and brachial endothelial function in young adults born SGA

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Small birth size is known to associate with later cardiovascular disease risk. Carotid artery intima-media thickness (IMT), endothelial function and high sensitive CRP (hsCRP) are thought to predict cardiovascular events. The aim of our study was to determine whether small birth size affects endothelial function and carotid artery IMT by 20 years of age in subjects born small for gestational age (SGA). Thirty-five SGA subjects and their 35 age- and sex-matched appropriate for gestational age (AGA) control subjects were studied at 20 years of age. We examined carotid artery IMT, casual BP, serum concentrations of lipids and hsCRP, and endothelial function by brachial artery flow mediated dilatation (FMD). The mean values of FMD and IMT did not differ between the SGA and AGA groups (9.46 vs 9.14 %, p=0.682; 0.43 vs 0.44 mm, p=0.502, respectively), the differences remaining insignificant even when adjusted for cigarette smoking, BMI and sex. The means of serum hsCRP concentrations did not differ between the groups (2.68 vs 2.11 mg/l, SGA vs AGA, p=0.473). No significant differences were found in the BP levels between the SGA and AGA groups either (systolic means 123.8 vs 123.4 mmHg, p=0.752; diastolic means 74.4 vs 75.9 mmHg, p=0.222, respectively). In the SGA group, cigarette smoking and higher diastolic BP associated independently with higher IMT in the logistic regression analysis [OR (95% CI)
Sex difference in BMI development modulates insulin sensitivity in extremely low birth weight infants during childhood

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Background: Advances in neonatal medicine led to increased survival rates of extremely low birth weight infants (ELBW, birth weight < 1000g). Several studies suggested that infants born prematurely are at increased risk to develop metabolic abnormalities.

Objective: ELBW small-for-gestational-age who (SGA) compared to those being appropriate-for-gestational-age (AGA) may have an even increased risk to develop metabolic disturbances. Catch-up in growth might have negative impact on insulin sensitivity.

Methods: We investigated the effect of birth weight (SGA vs AGA), gender, and catch-up in growth in ELBW infants on hormonal and metabolic parameters. We studies 63 ELBW children (mean age 5.8 years), 52 AGA and 11 SGA (birth length or weight < -2SD).

Results: 48 showed catch-up growth, reaching a height within a range of 1 SD from target height. We found no significant differences for fasting insulin, glucose, HOMA and IGFBP-1 between ELBW-AGA and ELBW-AGA. DHEAS levels were higher in the SGA group (median 464 ng/ml, range, 150-1030 vs 193, range 150-1270, p<0.001). Children with catch-up in growth had significantly lower IGFBP-1 concentrations (mean 38.5 ng/ml (SD 28.7) vs 34.9 (19.8), p=0.05). Consistently, we found lower IGFBP-1 in girls responding to the observed sex difference in weight development: girls had normalization of BMI from the age of 2 years whereas boys remained at a mean BMI of -1.96 SDS.

Conclusion: Metabolic and hormonal parameters in ELBW children are modulated by birth weight, subsequent catch-up in growth and weight, and sex-dependent weight development, resulting in measurable differences already in early childhood.

Psychiatric and cognitive outcomes in children and adolescents born small for gestational age

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Objective: Term small for gestational age (SGA) children and adolescents are at increased risk for mild cognitive deficits, hyperactivity, attentional problems and poor school performance. We evaluated behavioral, attentional problems and cognitive function in children and adolescents born SGA.

Methods: Fifty-one SGA children and adolescents were compared with fifty AGA subjects on psychiatric symptoms using Korea-Child Behavior Check List(K-CBCL). Korea-Youth Self Report(K-YSR) and Attention Deficit Hyperactivity Disorder Rating Scale(ADHDRS). Cognitive functions were estimated by Wechsler Intelligence Scale(K-WISC-III).

Results: Pubertal SGA adolescents showed higher delinquent, aggressive behavior, anxious and depressed scores(P<0.05), but psychiatric symptom scores were not different in prepubertal SGA and AGA groups. The SGA group had higher ADHDRS score than in AGA group but it was not significantly different. The prepubertal SGA group showed significantly lower verbal IQ (98.4±11.7 vs. 109±14.3, P=0.034), and verbal comprehension(98.4±10.9 vs 108.5±13.3, P=0.031) than in AGA group. The pubertal SGA group showed significantly lower verbal IQ, full IQ score, verbal comprehension and attention than in AGA group(P<0.05).

Conclusion: Term SGA adolescents experience more emotional and behavioral problems than AGA group. Verbal subscale was significantly lower in SGA group than in AGA group, and verbal than performance subscale was more affected.

Idiopathic precocious puberty (IPP) in girls: Clinical, endocrinological and ultrasonographic evaluations according to auxological data for gestational age

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Literature data report significant hormonal differences between children born small (SGA) or appropriate for gestational age (AGA), at the physiological onset of puberty. Moreover in SGA patients a correlation between neonatal weight, postnatal growth, pubertal development and insulin sensitivity has been found. Aim of our study was to evaluate possible correlations between sonographic, hormonal and metabolic parameters in IPP girls according to neonatal auxological data.

Forty girls with IPP (B2, Ph2), diagnosed by GnRH test (peak LH >7 mU/mL and pelvic sonography (ovarian volume >2 cc) were included in the study and subdivided in two groups: 1) 20 pts AGA) and 2) 20 pts SGA), well-matched for chronological age, bone age/chronological age ratio, body mass index. In all girls a blood samples were taken in order to determine: 17-beta-estradiol (E2), testosterone (T), inhibin B, IGF1, insulin and glucose (HOMA-IR); FSH and LH basal and after GnRH test; 170HP basal and after ACTH test. Statistical analysis was performed and data were expressed as mean and standard deviation score (M±SDs). Student’s t test was performed and p<0.05 was considered significant.
Children born small for gestational age (SGA):

**Metabolic risk**

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**Introduction:** Recent studies have shown that, the Metabolic Syndrome (MS) occurs more frequently among children who were born small for gestational age (SGA). Postnatal rapid weight gain has been associated with increased risk for metabolic diseases. The aim of our study was to investigate metabolic disorders in SGA children.

**Patients and Methods:** Sixty-eight Italian children born SGA in our Institute divided into 3 groups: A) 5-8 yr, n=20 pts; B) 9-13 yr, n=35 pts C)14-17 yr, n=13 pts. We evaluated: 1) catch up weight (CUW) as a weight gain from 3rd percentile of birth to > 50th percentile at the moment of the study. 2) MS ≥3 risk factors for metabolic diseases. The MS diagnosis SGA depends on the reference used. The equal percentage of low BW and BL using Nik compared to the much higher % of “low BL” than “low BW” according to UMcL suggests that the Nik reference is superior, confirming the effect of the choice of birth size reference on differentiating between SGA and ISS. As in many countries recent national references are unavailable, an old US reference, based on only 300 cases (Usher & McLean, 1969, UMcL) is often used, although a more recent Swedish reference (Niklasson, 1981, Nik) based on 475,000 cases seems more appropriate. To assess the effect of the choice of birth size reference on differentiating between SGA and ISS, we calculated birth weight and length SDS for both references in a group of 199 short but otherwise healthy children attending a single growth clinic. We also calculated head circumference (HC) SDS at birth with both references. According to Nik 47 (25%) patients were SGA (19% low BW, 21% low BL, 60% both low), and according to UMcL 50 patients (4% low BW, 44% low BL, 52% both low), suggesting that the -2 SDS cut-off for BL in UMcL is too high and for BW too low. 43 patients were classified as SGA with both references. For HC at birth (n=141), according to Nik 16 patients (14 SGA, 2 ISS) had microcephaly (HC < -2 SDS) (11%) and according to UMcL 32 patients (24 SGA, 8 ISS) (23%), including all patients with microcephaly according to Nik. This suggests that the cut-off for a small HC according to the UMcL reference is too high. In conclusion, we have shown that the diagnosis SGA depends on the reference used. The equal percentage of low BW and BL using Nik compared to the much higher % of “low BL” than “low BW” according to UMcL suggests that the Nik reference is superior, confirming the effect of the choice of birth size reference on differentiating between SGA and ISS. As in many countries recent national references are unavailable, an old US reference, based on only 300 cases (Usher & McLean, 1969, UMcL) is often used, although a more recent Swedish reference (Niklasson, 1981, Nik) based on 475,000 cases seems more appropriate. To assess the effect of the choice of birth size reference on differentiating between SGA and ISS, we calculated birth weight and length SDS for both references in a group of 199 short but otherwise healthy children attending a single growth clinic. We also calculated head circumference (HC) SDS at birth with both references. According to Nik 47 (25%) patients were SGA (19% low BW, 21% low BL, 60% both low), and according to UMcL 50 patients (4% low BW, 44% low BL, 52% both low), suggesting that the -2 SDS cut-off for BL in UMcL is too high and for BW too low. 43 patients were classified as SGA with both references. For HC at birth (n=141), according to Nik 16 patients (14 SGA, 2 ISS) had microcephaly (HC < -2 SDS) (11%) and according to UMcL 32 patients (24 SGA, 8 ISS) (23%), including all patients with microcephaly according to Nik. This suggests that the cut-off for a small HC according to the UMcL reference is too high. In conclusion, we have shown that the diagnosis SGA depends on the reference used. The equal percentage of low BW and BL using Nik compared to the much higher % of “low BL” than “low BW” according to UMcL suggests that the Nik reference is superior, confirming the effect of the choice of birth size reference on differentiating between SGA and ISS. As in many countries recent national references are unavailable, an old US reference, based on only 300 cases (Usher & McLean, 1969, UMcL) is often used, although a more recent Swedish reference (Niklasson, 1981, Nik) based on 475,000 cases seems more appropriate. To assess the
too high, and considering that reliable birth length measurements are difficult to obtain, a low BL (UmCL) seems a poor qualifying criterion for SGA. Also for the assessment of HC, the UmCL reference appears inferior.

Low birth weight is associated with higher risk of late metabolic consequences. Aim: to describe the postnatal growth, hormonal and metabolic status in children born small for gestational age (SGA) at prepubertal age. Methods: 51 small (SGA, birth weight and/or length < −2 SDs below the mean) and 95 appropriate-for-gestational age (AGA) children born after 32-42 weeks of gestation in Kaunas University Hospital in 1998-2000 were measured at birth, 12, 24 months and at 6 years of age. Lipid profile, insulin and adiponectin concentrations were assessed for all study children at 6 years of age. Results: At birth, 12, 24 months and 6 years of age SGA children were significantly shorter (p<0.001) and lighter (p<0.001) than AGA. However, waist-to-hip ratio and gain in BMI from birth to six years were higher in SGA as compared to AGA children (p<0.01). After adjustment for sex and BMI, SGA children had higher fasting cholesterol (p=0.032) and LDL-cholesterol (p=0.02) levels than AGA. Fasting insulin levels and HOMA-IR were also higher in SGA compared to AGA children (6.0±0.6 vs. 4.3±0.5 pmol/L, p=0.041 and 1.4±0.2 vs. 0.9±0.2, p=0.07, respectively). Adiponectin concentration was lower in SGA than AGA children (7.6±4.6 vs. 10.5±6.4 µg/ml, p = 0.006). In a linear regression model, HOMA-IR was related to weight gain from 2 to 6 years of age, analyzing in both groups combined (r² = 0.17, p<0.001) and in the SGA group separately (r² = 0.29, p=0.007). Conclusions. Though SGA children remained shorter and lighter at six years of age, a tendency for central pattern of fat distribution, higher fasting insulin, lower adiponectin levels and worse lipid profile might predispose eventual long-term metabolic complications in these individuals. Association between low birth weight and insulin resistance may be dependent on weight gain during the early postnatal years.

The relationship between thyroid function and obesity has been previously studied, but it is not completely clarified and conflicting data indicate no difference in thyroid pattern but also higher serum TSH and T3 in obese subjects compared to normal-weighted controls. Moreover, associations of insulin resistance and TSH levels has been recently reported in adults. The aim of the study was to investigate possible interplay between thyroid function, body composition and insulin resistance in Italian obese children and adolescents. Aim: to retrospectively re-evaluate a population of selected infants with congenital hypothyroidism (CH), in order to investigate whether sexual dimorphism affects: a) CH aetiology; b) its biochemical severity at the time of screening and recall; c) patients' biochemical response to replacement treatment during the 1st year of life; d) their bone maturation (BM) at birth; e) their psychomotor status at 6 years. This retrospective study covers a population of 192 infants (116 females) who were selected from a larger study performed at Kaunas University Hospital in 1998-2000. Results. Low birth weight and length are associated with congenital goitrous hypothyroidism. Thyroid peroxidase (TPO) deficiency can be diagnosed in the majority of cases with congenital goitrous hypothyroidism. TPO is a thyroid specific glycosylated hemoprotein. The TPO coding gene is localized on chromosome 2p25 and consists of 17 exons. Inactivating mutations in the TPO gene prevent iodination of tyrosine residues in thyroglobulin and therefore the assembly of thyroid hormone. We report a 16 years old boy, who was assigned to our clinic at the age of fourteen days with severe hypothyroidism and goiter. The biochemical parameters showed very low levels of T3 0.3 (1.2-2.8) µg/ml and T4 70 (90-200) ng/ml, very high levels of TSH 200 (1.4-8.7) µU/ml and T4G 441 (< 35) ng/ml. The thyroid volume was enlarged with 4.5 ml. The patient developed an expanding multinodular goiter from the age of ten despite adequate thyroid hormone substitution. Currently the enlarged volume of the goiter is 5.15 ml. The biggest node covers 1.81x1.81x1.8 cm. Scintigraphy showed an increased 123I-uptake but no evidence for malignancy. Thyroidectomy is planned. Gene analysis identified one of the most common mutations and one novel mutation in the TPO gene. The first mutation is the GCCG duplication in exon 8 at nucleotide position 1227. This creates a frameshift leading to a premature stop codon. The novel mutation c.2162 G>A in exon 12 results in a substitution of cysteine with tyrosine at position 721 (p.C721Y). Both mutations alter the hemo-peroxidase domain of TPO. This report underlines the importance of a careful and regular follow-up of patients with thyroid dysshormonogenesis. As pediatric patients with goitrous hypothyroidism caused by TPO gene mutation may develop thyroid cancer, thorough clinical and molecular investigation is warranted. In some cases thyroidectomy may be the ultimate cure for goiter.

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0.13, p<0.05), FM/LM (r= 0.14, p<0.05) and FM (r= 0.15, p<0.05) and nega-

tively with BMI (r=-0.18, p<0.01), basal IRI (r=-0.17, p<0.01), HOMA (r=-

0.15, p<0.05). In conclusion, the positive correlations between TSH and IRI,

HOMA, FM and FM/LM in obese euthyroid children and adolescents confirm

previous reported data in adulthood. The negative correlation of FT4 with

BMI, and conversely, the positive correlations with FM/LM and FM, together

with the lack of correlation between FT3 and BMI suggest the hypothesis of

primary alterations in thyroid function in obese children and adolescents.

Newborn screening for congenital hypothyroidism (CH) has been widely ad-

opted as early detection and treatment of CH prevents the severe neuro-co-

gnitive deficit found in untreated patients. Despite extensive research into IQ

scores in CH during childhood there is little information on adult outcome in

terms of pragmatic measures such as educational achievement, employment,

residency and relationships. We present the results of a questionnaire-based

study examining these outcome measures in Scottish adults born between

1979 and 1989, and diagnosed with permanent CH on newborn screening.

The unaffected siblings of our patients served as controls, to counter socio-

economic confounders. Matched patient and sibling pairs were compared.

Validated systems were used to score education and employment data. Where

possible, responses were compared with population normative data. There

were 155 eligible patients. 79 have returned questionnaires to date, together

with 34 sibling controls. Median age (range) and sex ratio (M:F) of patients and

siblings was 175 (0-264) and 226.5 (0-264) respectively (p=0.7). Comparison

of median (range) education scores in severe CH at diagnosis (total T4 < 43.0

nmol/L) with milder cases showed similar scores - 203 (0-330) versus 231

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We have been unable to find a difference between patients with permanent CH and their siblings in terms of educational or relationship outcomes, or between severely affected patients compared with mildly affected patients. Further analysis is required to examine if subtle neuro-cognitive deficits in CH affect patients’ prospects for employment and independent residence.

**P2-d2-549 Thyroid 2**

Evaluating the effectiveness of thyroxin alone and with prostaglandin E2 and vitamin D and calcium gluconate on orthodontic tooth movement and root resorption in rat

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With the role of thyroid in regulating bone remodeling activities, the purpose of this experimental study is evaluating the effectiveness of thyroxin hormone alone and with prostaglandin E2, calcium gluconate and vitamin D on Orthodontic Tooth Movement(OTM) and Root Resorption (RR). Rats were randomly divided into 9 groups (n=8). Thyroxin 2.0 μg/kg, Thyroxin 3.1 μg/kg, Thyroxin 2.0 μg/kg + prostaglandin E2 and/or vitamin D3, Thyroxin 2.0 μg/kg + prostaglandin E2+ calcium gluconate and vitamin D3. The duration of the study was 2 days. Tooth movement was measured by evaluating the distance which was occurred between the first molar and with US pattern of thyroiditis. The solutions were injected intra peritoneal. On the 7th day injections have done as same as the zero day for those groups. On the 14th day only thyroxin injection has done. The duration of the study was 21 days. Tooth movement was measured by evaluating the distance which was occurred between the first molar and second molar in upper right quadrant by special gauge 0.01 accuracy. In order to study the data and do the statistical calculations the One-Way ANOVA method was used. Also for more accurate in evaluation we used Student-Newman-Keuls method. In this study the most OTM (Mean 0.82755 mm) was seen in 6th group, which had a significant statistical difference with the 3th, 4th, 7th, 8th, 9th and 10th(p<0.001) and 5th(p<0.01) and 7th(p<0.05). The 4th group (Mean OTM 0.7375 mm) had a significant difference with the 3th, 8th(p<0.001) and 1th(p<0.01) and 2th(p<0.05). The 5th group (Mean OTM 0.59mm) had a significant difference with the 3th and 8th(p<0.01) groups. In the other groups there was no significant difference in OTM. Also there was no significant statistical difference in all groups in RR. These results suggested that thyroxin, calcium gluconate, prostaglandin E2 and Vit D played a major role in orthodontic tooth movement, which is important in orthodontic treatments in pediatrics.

**P2-d2-550 Thyroid 2**

Clinical description of a large cohort of infants with congenital hypothyroidism and iodide organisation defects

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Iodide organisation defect (IOD) could lead to congenital hypothyroidism (CH) with normal sized gland but incidence is unknown. Some genes encoding for key factors in homogenogenesis have been involved (as thryopexyse or DUOX) but no genotype-phenotype correlation could be made so far. Thus, the aim of the present study was to describe the precise phenotype of a large group of children with CH and iodide organisation defect (IOD), suspected on the basis of a normal sized gland and an abnormal perchlorate discharge test (PDT), as the first step of a project evaluating correlations between phenotypes and molecular abnormalities.

**Population and Methods:** 71 children born in Paris between 1980 and 2006 were contacted. Two groups of patients were defined according to the result of PDT: total IOD (TIOD) and partial IOD (PIOD) when the release was above 90% or between 10 and 90%, respectively. Comparisons between groups were performed using SPSS 14.0 for Windows.

**Results:** Restricted to the period 2003-2006, IOD was identified in 13.6% of CH children (Incidence 1:20,660). Of the 71 studied children with IOD, congenital goiter was present in only 50 to 60% of patients. According to the PDT results, 61 had PIOD and 10 TIOD. Most of TIOD patients presented a permanent CH characterized by severe clinical presentation, whereas PIOD children had a wide spectrum of clinical characteristics from total absence to severe symptoms. Evolution showed transient hypothyroidism in 1 TIOD (10%) and 16 PIOD (16%) patients.

Conclusion: Severe presentation in the majority of TIOD patients suggests that TIOD could be related to dysfunction of one key enzyme of homogenogenesis. In contrast, the various clinical characteristics of PIOD children suggest that PIOD might be related to various mechanisms, either reduce enzymatic activity or defects in iodine storage and release.

**P2-d2-551 Thyroid 2**

Thyroid status in children and adolescents after bone marrow transplantation (BMT), with and without total body irradiation (TBI) conditioning

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Thyroid dysfunction after BMT may be related to TBI toxicity or to chemotherapeutic agents as busulphan and cyclophosphamide. The aim of the study is to evaluate the incidence of thyroid abnormalities in a series of transplanted children and adolescents and its possible relationship with the type of conditioning. 65 patients (40 M, 25 F) underwent BMT for childhood malignancies at median age of 8.3 years (range 0.8-18.4 yrs). The BMT conditioning was TBI (800-1200 cGy) in 14 pts (Group A), high dose chemotherapy in 51 pts (Group B): busulfan (BUS), cyclophosphamide (Cy), Melphalan (I-PAM), TSH, FT3, FT4, i-peroxycy thyroidog (TPO) thyroidglobulin (TG) autoantibodies (ab) and thyroid ultrasonography (US) were evaluated during follow-up (7.4 yrs, range 2-22 yrs). 26/65 pts developed subclinical hypothyroidism (SH), with a median time of onset of 2.1 years post-BMT (0.2-11). SH is higher in group A (64%) than in group B (33%). Anti TPO/TG ab were detected in 29 of 51 patients (57%) in Group B and 15 of 14 patients (105%) in group A. In group A 33 patients (65%) had SH, 12 patients (23%) had mild SH and 2 patients (4%) had severe SH. In group B 12 patients (23%) had SH, 3 patients (6%) had mild SH and 1 patient (2%) had severe SH (TSH > 10 mIU/l). SH was observed in 22 patients (34%) in group A and 10 patients (19%) in group B. Anti TPO/TG ab were found in 4 patients (6%) in group A and 5 patients (9%) in group B. The percentage of SH in patients with subclinical hypothyroidism is 61% (range 50-90%) with the highest incidence in patients treated with and without total body irradiation (TBI). The incidence of thyroid abnormalities was lower in patients treated with US pattern of thyroiditis. Anti TPO/TG ab were found in 2 patients (4%) in group A and 3 patients (6%) in group B. The percentage of SH in patients treated with US pattern of thyroiditis is 61% (range 50-90%).

Table. Pts with subclinical hypothyroidism (values are median and range in brackets)

<table>
<thead>
<tr>
<th>SH pts</th>
<th>N%</th>
<th>Age at BMT (yrs)</th>
<th>BMI (kg/m)</th>
<th>TSH ULN</th>
<th>TPO+TG (mIU/l)</th>
<th>i-thyroxine (lU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>26/65</td>
<td>6.4</td>
<td>(3.3-14)</td>
<td>15</td>
<td>16</td>
<td>10.8</td>
</tr>
<tr>
<td>Group A</td>
<td>9/14</td>
<td>7.6</td>
<td>(3.5-13)</td>
<td>16</td>
<td>14</td>
<td>10.7</td>
</tr>
<tr>
<td>Group B</td>
<td>17/51</td>
<td>3.5</td>
<td>(0.8-12)</td>
<td>15</td>
<td>14</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Subclinical hypothyroidism is the most frequent thyroid abnormality found in our study. Interestingly the incidence in Group B is higher than reported by literature. The prevalence of anti TPO/TG ab in these patients suggests autoimmune pathogenesis of thyroid hypofunction, that may progress. Whether this condition may be related to bone marrow donor autoimmune status or toimmune pathogenesis of thyroid hypofunction, that may progress. Whether this condition may be related to bone marrow donor autoimmune status or toimmune pathogenesis of thyroid hypofunction, that may progress.
Antithyroid drugs (ATD) are usually recommended for first-line treatment of hyperthyroidism in children. However, the choice between drug-based and alternative therapies (surgery/radioactive iodine) after an initial course of ATD remains controversial. In this prospective multicentre cohort study of 154 patients with GD, diagnosed at a median age of 12 years and included from 1997 to 2002, the relapse rate two years after the end of the first course of ATD was 68%. Duration of the initial course of ATD, ethnic origin, age and severity of the disease at diagnosis were identified as predictors of the risk of relapse potentially useful for guiding management decisions (ESPE 2007). This study was continued, to determine remission rates after a second course of ATD. This course was initiated at a median age of 14.3 years for the 108 patients who relapsed after the end of the first two-year course of ATD. The relapse rate after discontinuation of this second course of 2 years was 81% (95% CI:69-91%), and median time to relapse was 2 months. Fifteen patients were still in remission after a median follow-up of 38 months. The proportions of patients in remission after discontinuation of the first and second courses of ATD were 27% and 19%, respectively. In total, 64 of the patients of the initial cohort are currently in remission; the others are on ATD (n=67) or have had surgery (n=2) or have been lost to follow-up (n=13). In conclusion, administering a second course of ATD may be beneficial, leading to remission in an additional 19% of children. It remains unclear whether longer periods (>2 years) of primary ATD treatment, by keeping patients euthyroid for longer, have a better impact on outcome than two independent two-year courses separated by a hyperthyroid relapse. This hypothesis requires testing in large prospective randomised trials. 

Objective: In the textbooks, hypothyroidism is expressed to be a condition associated with elevated concentration of sweat chloride content. However, there are no adequate studies in literature. The aim of this study is to investigate whether congenital hypothyroidism affects amount and chloride content of sweat in "quantitative pilocarpine iontophoresis sweat test" (QPIT)

Methods: Patients who had congenital hypothyroidism and were otherwise healthy were included into study. Thyroid stimulating hormone (TSH); thyroxine (T4); free T4; triiodothyronine (T3); free T3; and antibodies against thyroglobulin (anti-TG) and thyroid peroxidase (anti-TPO) at referral were determined by immunoassays. Thyroid sonography and scintigraphy were performed to all patients. The patients were treated with Na-L-thyroxin (100 mcg/m2/d, single dose). QPIT in all patients was made in both hypothyroid and euthyroid state.

Results: The study was completed with 18 patients. All patients did not previously receive thyroid hormone-replacement therapy. The median (range) chronological and bone age at referral were 57.30 (12-144) months and 13.30 (3-48) months, respectively. Thyroid auto-antibodies were not present in all patients. Of the 18 patients, 9 (50%) had ectopic thyroid tissue, 6 (33%) had agenesis of the thyroid gland, and 3 (16%) had gland hypoplasia. The median time for euthyroid state was 2.3 (1-4) months. The serum concentrations of thyroid hormones changed during Na-L-thyroxin therapy and the results of QPIT performed in hypothyroid and euthyroid state are shown in the Table.

Markers Hypothyroid state Euthyroid state p
T3 (ng/mL) 0.45 ± 0.27 1.87 ± 0.56 0.001
T4 (mcg/dL) 1.26 ± 0.59 12.08 ± 4.94 0.001
FT3 (pg/mL) 1.23 ± 0.63 5.30 ± 3.30 0.001
FT4 (ng/dL) 0.14 ± 0.0 2.68 ± 1.87 0.001
TSH (uIU/mL) 100 ± 0.0 5.52 ± 2.28 0.001
Sweat (mg) 103.30 ± 56.46 104.30 ± 63.04 Non significant
Sweat Cl (mmol/L) 37.90 ± 15.47 33.60 ± 13.66 Non significant

Conclusion: Our findings indicate that congenital hypothyroidism does not affect amount and chloride content of the sweat in QPIT.

Objective: The purpose of the study was to evaluate the prevalence of hypothyroidism and its effect on height and weight of German children with Down syndrome.

Methods: We evaluated 62 patients with Down syndrome. We determined thyroid hormones (TSH, T4, T3, T4u), TSH-stimulated TRH test, antithyroid antibodies and performed thyroid sonography.

Results: The prevalence of hypothyroidism was 7.5% (95% CI: 3.1-14.8%). The mean TSH levels were significantly increased in comparison to a reference population (p<0.001). There was no difference in the prevalence of hypothyroidism between the sex groups (p=0.99). A significant correlation was found between the TSH levels and the age of the children (p<0.001). Thyroid sonography revealed hypoechogenic thyroid glands in all hypothyroid patients.

Conclusion: Hypothyroidism is common in children with Down syndrome. The prevalence of hypothyroidism may increase with age.
was 73.3%±19.4%; and, the mean 24-hour I-123 uptake was 79.3%±12.6%.

The dose of I-131 administered was calculated by the radiologist as follows: 240 microcuries per gram of thyroid tissue, divided by the 24 hour uptake. The actual mean dose administered was 17.5±9.3 millicuries. Every patient had labs confirming a successful ablation at the time of their first lab draw post-ablation. This was at an average of 61±32 days post-ablation.

Two of the patients (88%) only had one endocrinology office visit between diagnosis and the ablation procedure; the other three patients had two visits. All patients had between 1 and 3 pediatric endocrine visits per year from the time of diagnosis. Thyroid ablation therapy for pediatric Graves disease is a safe, efficacious, and efficient therapy, and should be considered the standard of care in the 21st century.

Two common forms of autoimmune thyroid disease (AITDs) are Graves’ disease and Hashimoto’s thyroiditis. Cytotoxic T lymphocyte antigen 4 (CTLA4) encoded by the CTLA4 gene on chromosome 2q33 plays a role in susceptibility to Graves’ disease and also probably important for Hashimoto’s thyroiditis as well as for other endocrine autoimmune disorders. The CTLA4 locus is the only non-human leukocyte antigen (HLA) locus for which association with Graves’ disease has been demonstrated repeatedly. Particularly, association of the three polymorphic markers of CTLA4 gene, namely C(-318)T, A49G and (AT)n dinucleotide repeat, with the Graves’ disease was demonstrated in most population-based investigations. Although there are few studies to reveal the association of markers with Hashimoto’s thyroiditis. A49G polymorphism proposed to be associated with Hashimoto’s thyroiditis as well as for the other endocrine autoimmune disorders. The CTLA4 gene polymorphisms of C(-318)T; A49G and (AT)n dinucleotide repeat, with the Graves’ disease was demonstrated in most population-based investigations. Although there are few studies to reveal the association of markers with Hashimoto’s thyroiditis. A49G polymorphism proposed to be associated with Hashimoto’s thyroiditis and C(-318)T was suggested to be not associated. This study included children and adolescents with AITDs treated at our outpatient clinic between 2000 and 2007. The patient groups consisted of 88 patients (10 males, 78 females; mean age 14.5±3.2 years (4.6-21.0 years)) with a previous diagnosis of AITDs. 119 euthyroid volunteers (51 males and 61 females; 14.1±2.9 years (5.2-18 years)) were. In this study we have investigated these two polymorphic markers and documented that the A49G polymorphism may increase the susceptibility for Hashimoto’s thyroiditis.

A rising incidence of congenital hypothyroidism (CHT), reports of an association between thyroid function and risk of metabolic disease and debate regarding TSH screening threshold prompted us to examine: 1) the incidence of CHT in Northern England; 2) the relationship between TSH and birth-weight in the population and 3) the impact of TSH threshold on the need for repeat testing in infants born pre-term. 30-35,000 infants are screened each year in a single centre by measuring blood spot TSH levels (AutoDelfia). Preterm infants (<35w gestation) undergo repeat TSH screening at 36w. We examined the incidence of CHT over a period of 11y (1994-2005) and compared TSH levels with birth-weight, gestational age and sex in a 10% sample of all infants screened between April 2005 and March 2006. We also studied the number of false positives and false negatives on initial screen (TSH threshold <6mU/l) in preterm infants over a 2y period (April 2005-March 2007) by comparing the first and second TSH values. Between 1994 and 2005 there were 212 cases of CHT. Incidence increased significantly over the study period (p< 0.0001) from 37 per 100,000 in 1994 to a peak of 92.8 in 2003. Fractional polynomial regression analysis in the population as a whole showed a significant association between TSH and birth weight (p<0.0001) and sex (p=0.02) but not gestational age (p=0.37). Out of 2039 preterm infants who had a repeat test, all the infants whose TSH was <6mU/l on first sampling had a subsequent TSH of <10mU/l and none are on long-term thyroxine therapy. 1. The incidence of CHT in Northern England is rising. 2. TSH levels are inversely related to birth-weight in the neonatal period. 3. Reducing the TSH screening threshold may mean that repeat testing of preterm infants is no longer appropriate.

Thyroid function and size are, in extension to tight genetic control, thought to be influenced by a number of anthropometric, endogenous and environmental factors. The aim of the study was to investigate determinants of thyroid volume in childhood. 823 children (338 girls, 485 boys) without known thyroid disease were examined, including ultrasound of the thyroid gland. Using immunoassays, all had determination of serum thy stimulating hormone (TSH), thyroid hormone (T4), free T4 (FT4), triiodothyronine (T3), and free T3 (FT3), while insulin-like growth factor 1 (IGF-1) and IGFBP-3 were determined in 666 individuals. Thyroid volume was calculated as the sum of maximal length*width*depth*0.52 of each lobe, using a well validated and accurate method. Values of serum TSH and thyroid volume were log-transformed to obtain normal distribution. Measurements of height, weight and BMI were included as age-specific SDS-values. Body surface area (BSA) was calculated a.m. Data were analysed by multiple linear regression analyses. Age-specific estimations of thyroid volume (geometric means ± 2SD) are shown in table 1.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N</th>
<th>Mean thyroid volume (ml)</th>
<th>-2SD (ml)</th>
<th>+2SD (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 - 4.9</td>
<td>63</td>
<td>2.1</td>
<td>1.1</td>
<td>3.9</td>
</tr>
<tr>
<td>5.0 - 5.9</td>
<td>113</td>
<td>2.5</td>
<td>1.5</td>
<td>4.0</td>
</tr>
<tr>
<td>6.0 - 6.9</td>
<td>215</td>
<td>2.8</td>
<td>1.6</td>
<td>5.1</td>
</tr>
<tr>
<td>7.0 - 7.9</td>
<td>227</td>
<td>3.2</td>
<td>1.9</td>
<td>5.4</td>
</tr>
<tr>
<td>8.0 - 8.9</td>
<td>144</td>
<td>3.5</td>
<td>2.0</td>
<td>6.1</td>
</tr>
<tr>
<td>9.0 - 9.9</td>
<td>54</td>
<td>3.7</td>
<td>2.1</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Thyroid volume was significantly positively correlated to age, body surface area, and serum IGF-1 (r=0.101, p=0.031; r=0.388, p<0.001; r=0.135, p=0.001), but not to gender. In a model including height SDS, weight SDS, BMI SDS and BSA, only BSA remained significantly associated to thyroid volume. FT4 was positively and serum TSH negatively correlated to thyroid volume (r=0.118, p<0.001; r=-0.080, p=0.014, respectively), in a model including height SDS, weight SDS, BMI SDS and BSA. Our results support previous data from adults that the thyroid and growth hormone axis are closely interlinked as thyroid volume in children was strongly correlated, not only to age and anthropometric values, but also to serum IGF-1.
Objective: To evaluate the effect of different initial L-thyroxine (L-T4) replacement doses on intellectual outcome (IQ) in patients with congenital hypothyroidism (CH) detected by neonatal screening program. Patients and methods: The IQ was evaluated at 8 years of age in 61 patients with CH by the WISC-R test. The patients were divided into 2 groups according to the initial L-T4 dose: Group A (n=25) received a mean initial L-T4 dose of 9.0±0.6 µg/kg/day (range 8.0-10.0) and Group B (n=36) received a mean initial L-T4 dose of 13.0±1.5 µg/kg/day (range 10.1-15.0).

Results: The Full-scale IQ (FSIQ) and Performance IQ (PIQ) were similar in the 2 groups (FSIQ: Group A 94.2±3.5; Group B 98.6±2.4; PIQ: Group A 98.5±3.3; Group B 97.6±2.9). The Group B treated with a higher initial L-T4 dose showed a slightly better Verbal IQ (98.7±2.0) compared with Group A (91.8±3.0; p=0.005). There were not significant differences between the two groups in the chronological age, duration of and severity of hypothyroidism at the time of diagnosis. After the first month of treatment optimal serum levels of thyroid hormones were achieved by both groups, whereas only patients from group B showed a mean serum TSH levels within normal range (1.7±0.5mIU/l vs 8.7±2.9, p=0.007). Despite the high initial L-T4 dose 7/36 patients (19%) from Group B presented a FSIQ < 85 (vs 8/25 (32%) patients from Group A, p=ns).

Conclusions: results indicate that the majority of patients with CH treated in the first weeks of life achieved a normal IQ at 8 years. The initial L-T4 dose between 10 and 15 µg/kg/day seems to be associated with a slightly better verbal outcome and with a lower number (although not significant) of subnormal IQ. It should be pointed out however, that globally 25% of our patients with CH showed a subnormal FSIQ despite an adequate initial treatment and a close follow-up, thus suggesting that other factors may interfere with a normal intellectual outcome.

P2-d2-561 Thyroid 2

Effect of treatment with thyroxine on goiter size in euthyroid children with Hashimoto's thyroiditis

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Background: There is no consensus whether euthyroid children with Hashimoto’s thyroiditis (HT) need treatment with thyroxine. Objective: To assess whether thyroxine influences goitre progression (calculated thyroid volume on U/S scan) in euthyroid children with HT. Patients and methods: We studied 50 euthyroid children with HT for a two year period. Twenty five children (17 girls), median age 12.1 (11.1-13.4) yrs were randomised to receive thyroxine and 25 children (20 girls) age 12.2 yrs (11.1-13.0) did not receive treatment and were followed-up.

Results: There were no significant differences in sex, age, height SDS, weight SDS, BMI SDS and thyroid volume SD 1.1 (0.7-1.5) and 0.9 (0.4-1.4) respectively between the two groups. Following one year there was no significant difference in the thyroid volume 7.1 (5.8-10.2) and 9.0 (7.9-10.6) ml respectively (p=0.126) and thyroid volume SD 1.0 (0.0-1.4) and 1.7 (0.8-2.0) ml (p=0.075) between the treated and the non treated group. Three children of the non treated group developed hypothyroidism and were treated were excluded from further analysis. Following two years the children on thyroxine had significantly smaller thyroid volume 7.6 (6.3-9.2) vs 10.6 (8.2-12.1) ml (p=0.016) and thyroid volume SD 0.6 (0.3-1.0) vs 2.0 (1.1-2.3) ml (p=0.001) compared to the children without treatment. When each group was studied separately and comparisons within groups were made, there was no significant difference in the thyroid volume nor in the thyroid volume SD before and after one year of treatment, however thyroid volume SD was significantly lower two years following treatment compared to the thyroid volume before treatment (p=0.002, Wilcoxon signed rank test). In the non treated group, thyroid volume and thyroid volume SD increased after the 1st year (p=0.0001) and p=0.007 respectively) and 2nd year (p=0.001 and p=0.006) of follow-up.

Conclusion: Treatment with thyroxine is beneficial for the further progression of goitre because it reduces thyroid volume significantly in euthyroid children with HT.

P2-d2-562 Thyroid 2

Thyroid dysfunctions in children detected in mass screening for congenital hypothyroidism

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Objective: 1. Assessment of the validity of 1st and 2nd verification in determining the prevalence of congenital hypothyroidism (CH) and hyperthyrotropinaemia (HT) and their fixed forms in newborns with TSH≥15uIU/mL in CH mass screening. 2. Analysis of causes in fixed CH and HT.

Methods: Of 155861 neonates with body weight≥2500g born in Malopolskie province between 2000-2004, CH mass screening identified 68 children with TSH≥15uIU/mL in blood on filter paper. Serum TSH and FT4 levels were de-
Hypothalamic-pituitary thyroid axis changes during the critical illness. To describe the thyroid function of the pediatric patient that suffers an acute critical illness, 37 children (mean age 7.56 years; range: 1.08-18.8, 62% boys, mean weight -0.29 SDS) that were admitted consecutively to the Intensive Care Unit (ICU) between July 2006 and May 2007 were studied. Levels of TSH, T4, T3 and FT4 by ECLIA method (Elecsys Roche), ATPO and ATG antibodies were measured at admission, 48 and 72 hours and weekly thereafter until their normalization. Children <1 year of age, with Down’s syndrome, hepatic or renal failure or those who underwent CNS surgery were excluded. PRISM score was calculated at admission. T4 and FT4 data from 51 healthy children, TSH levels from 129 healthy children and T3 levels from an historical cohort were used as controls. 4 patients showed normal thyroid profile, another patient had a primary hypothyroidism and 32 (86.5%) had low TSH levels at admission were lower than those of the control group and decreased levels of T3, T4 and FT4L without a compensatory increase of TSH. FT4 levels at admission were lower than control group in 75% of children with TSH≤15μIU/ml in mass screening. Based on 2nd verification, fixed of these disturbances confirms the diagnosis of CH or HT in 75% of children with TSH≥15μIU/ml. Others advised uncrushed or crushed and dry while 8 members gave no specific advice to parents. The initial daily dose of thyroxine, usually prepared locally, but only 7 respondents currently preferred using liquid T4. The majority of members, 89/103 (68.5%) recommended crushed tablet in 5ml liquid. Others advised uncrushed or crushed and dry while 8 members gave no specific advice to parents. The initial daily dose of thyroxine was variable: 33/128 (26%) were using 25 μg, 56/128 (44%) 37.5 μg, 2/128 (2%) 40 μg and 31/128 (24%) 50 μg. There is considerable variation in the initial management of CH amongst British paediatric endocrinologists. A consensus is required concerning the optimal age at first post-treatment visit - currently more than 10 days in 58%; and in the initial daily dose of replacement thyroxine, which is not consistently related to the infant’s weight or CH aetiology. We are in the process of developing a national protocol for both diagnosis and management of CH in order to standardise management in Scotland. We thank all the members of the BSPED for their patience and time in responding to the questionnaire.

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for the thyroid status in children with hypothyroidism on L-Thyroxine (L-T4) treatment.

**Patients and Methods:** Fifty-four patients with hypothyroidism (HT) (27M, 27 F; mean age: 9.1±5.5 yrs; primary HT 42, secondary HT 12) and 21 healthy age and sex matched controls (9M, 12F; mean age: 9.75±5.0 yrs) were included in the study. Serum TSH, FT4, serum CysC and creatinine (Cr) levels were studied in patients with hypothyroidism twice, in the euthyroid (on-L-T4) and hypothyroid state and in controls. Glomerular filtration rate (GFR) was calculated using Schwartz formula.

**Results:** FT4 and TSH levels were appropriately abnormal in the hypothyroid state and in normal ranges in the euthyroid state in the study group. Control group had normal FT4 (pmol/L) and TSH (mIU/L) values (17.7±2.1 and 3.1±1.1 respectively) which were similar to the values in euthyroid status of the children with hypothyroidism. Cr, GFR and CysC levels did not differ significantly between the control group and the respective values of the euthyroid status of the study group. Comparison of the hypo- and euthyroid status of the study group yielded higher Cr (p=0.002) and lower GFR levels (p=0.011) and lower CysC (mg/dl) in the hypothyroid status (0.64±0.14) than the values in the euthyroid status (0.67±0.0) (p=0.040). Comparison between the control group and hypothyroid status of the study group revealed similar differences in these parameters. CysC levels had positive correlation with T4 in hypothyroid status and euthyroid status (p=0.01 and p=0.03, respectively).

**Conclusions:** We demonstrated a major impact of thyroid dysfunction on cystic levels, but changes in serum CysC levels in hypo- and euthyroid status did not exceed the reference intervals. Serum CysC levels have limited use in determining peripheric effects of thyroid hormones.

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**P2-d2-566 Thyroid 2**

**Organizing a universal screening program for congenital hypothyroidism (CH): Issues in a developing country**

Anju Virmani, Uma Ravishankar, Vidya Gupta, Anjali Kulkarni, Sushma Kaul, Saroja Balan

1Indraprastha Apollo Hospital, Delhi, Pediatrics, New Delhi, India; 2Indraprastha Apollo Hospital, Nuclear Medicine, New Delhi, India.

CH screening is not universal in developing countries. We analyze retrospectively, our experience in a private tertiary care hospital catering to upper socio-economic group patients, in organizing a newborn screening program, and document the normal range of newborn TSH & FT4 in our (mildly iodine deficient) region. Discharge summaries, cross-checked with RIA records, yielded 3,809 newborns. Prior to 2003, screen policy was to test TSH & FT4 at discharge. Problems encountered were: discharge with "report awaited"; thus risk of remaining untreated if baby did not come for follow up; and need for specific designated program director to recall babies. After 2003, mandatory cord blood (CB) screening was started. Advantages: no needle prick; no need for specific designated program director to recall babies. After 2003, screen policy was to test TSH & FT4 at discharge. Problems encountered were: discharge with "report awaited"; thus risk of remaining untreated if baby did not come for follow up; and need for specific designated program director to recall babies. After 2003, mandatory cord blood (CB) screening was started. Advantages: no needle prick; no need for specific designated program director to recall babies. After 2003, mandatory cord blood (CB) screening was started. Advantages: no needle prick; no need for specific designated program director to recall babies. After 2003, mandatory cord blood (CB) screening was started. Advantages: no needle prick; no need for specific designated program director to recall babies. After 2003, mandatory cord blood (CB) screening was started. Advantages: no needle prick; no need for specific designated program director to recall babies.
It was aimed to compare the thyroid function tests performed in obese children and adolescents with those in healthy children. In the present study, the thyroid functions of 317 (173 females) children and adolescents, whose body mass indexes were over 95th percentile and who was diagnosed as exogenous obesity, and those of 100 children (50 females), whose body mass indexes were below 85th percentile and who had no endocrinologic problem and have been followed in our unit with the diagnosis of constitutional and/or familial short stature, were compared. There was no difference between the obese and control groups regarding age (11.09±3.43 and 10.47±3.89 years) and gender. The free T3, free T4, total T3, total T4, TSH, ATPO, and ATG levels, body mass indexes, and pubertal stages of all patients were recorded. The statistical analyses were performed by using nonparametric student’s t-test and chi-square test via SPSS, version 11.0. TSH and free T3 levels were found significantly higher (p=0.026 and p=0.035, respectively) while free T4 levels were detected significantly lower (p=0.026) in the obese group compared with the control group. TSH was higher than the upper limit in 18 cases (%5,67) of the obese group and 1 case (%1) of control group. In 4 of the 18 obese patients with elevated TSH level, ATG and/or ATPO positivity was detected and their thyroid ultrasonography findings were consistent with thyroiditis. Additionally, an exaggerated response to a TRH test was found in a case. In other cases, no pathology responsible for the elevated TSH level was detected. It is known that hyperalimentation increase T3 levels in healthy children; however, other cases, no pathology responsible for the elevated TSH level was detected. It is known that hyperalimentation increase T3 levels in healthy children; however, no pathology responsible for the elevated TSH level was detected.

**Discussion:** Due to the high risk of malignancy we recommend surgical removal of all thyroid nodules when malignancy cannot be ruled out. Occasionally, rare conditions like intrathyroidal thymic tissue can be identified to be the cause of a thyroid nodule. Practical guidelines for the management of solitary thyroid nodules in children are desirable.

**Conclusion:** We conclude, that intrathyroidal thymic tissue should be included into the differential diagnosis of solitary thyroid nodules. A brief review of the hitherto reported literature will be provided.
Suppressive therapy with thyroxine is an option for decreasing thyroid size in euthyroid goiter, but this therapy remains controversial. The efficacy of treatment with TSH-suppressive doses of L-thyroxine (T4; 36.8 to 113.1 micrograms/square meter/day) was assessed in 80 pediatric patients (65 females and 15 males) with simple, diffuse, euthyroid goitre in a retrospective clinical trial. Patients with clinical and subclinical hypothyroidism, hyperthyroidism, autoimmune thyroid diseases and nodular goiter were excluded. The response to treatment was assessed by both clinical and ultrasonographic examination of thyroid gland. Thyroid size was graded as grade I, II, III, IV and V. Factors possibly affecting the results of treatment were also evaluated. The ages of patients at diagnosis ranged from 3.69 to 15.26 years and the duration of suppressive treatment ranged from 6 months to 9.86 years. When evaluated by clinical examination, no patient had an increase in thyroid size (grade). 19 patients had unchanged thyroid size and the remaining 61 patients had decreased thyroid size. When assessed by ultrasonography, 11 patients were considered as unresponsive to suppressive treatment (thyroid volumes either unchanged or increased) and the remaining 69 patients considered as responsive (thyroid volumes decreased). Age; gender; baseline thyroid grades or volumes; initial serum TSH, total T4, total T3, free T4 and free T3 levels; the dosage of L-thyroxine treatment; and family history of thyroid diseases were found as unrelated to the efficacy of suppressive treatment (p<0.05). L-thyroxine was well-tolerated and there were no drug related side effects. In conclusion, L-thyroxine can be safely and effectively used in suppressing thyroid size in children with simple, diffuse, euthyroid goiter.

Suspicious reflections in Hashimoto thyroiditis in a girl

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1Haga Ziekenhuis/Juliana Children’s Hospital, Paediatrics, The Hague, Netherlands; 2Haga Ziekenhuis/Juliana Children’s Hospital, Radiology, The Hague, Netherlands

Case: A 13 year old girl presented with a small palpable mass located anteriorly of the thyroid gland. This was present for some weeks, sometimes painful and increased in size. Hoarseness, nor any other sign or symptom of thyroid disease was present. At physical examination no pathological lymph nodes were detected. The left lobe of the thyroid gland was increased in size, firm and smooth, non-nodular at palpation. At ultrasound the small mass appeared to be a lymph node. The thyroid gland was diffusely enlarged. The left lobe showed an inhomogeneous pattern with many reflections, mimicking small microcalcifications. A small nodular structure was observed near the isthmus.

Laboratory evaluation:::Free T4: 12.8 pmol/L, TSH: 3.5 mU/L, total T4: 97 nmol/L, T3: 2.2 nmol/L, anti-TPO antibody levels were strongly elevated, as were anti-Tg antibodies; TSHReceptor antibodies were not present. Calcium and phosphate levels were normal. Despite suggestive antibody levels, fine needle aspiration was performed from the parenchyma and the nodule under ultrasound guidance. Cytology revealed no malignant cells, but a pattern most likely associated with Hashimoto thyroiditis.

Discussion: Thyroid microcalcifications are associated with malignancy, either papillary or medullary carcinoma. In the literature we did not find cases of microcalcifications in Hashimoto thyroiditis in children. Most literature is devoted to intranodular microcalcifications in adults. In this child the diagnostic dilemma was due to the uncertain nature of the ultrasound findings.

Conclusion: This case report emphasizes the diagnostic difficulties in the interpretation of an ultrasound pattern suspect for microcalcifications in children with thyroid enlargement, either nodular of non-nodular. Fine needle aspiration has to be performed even in presence of suggestive antibody titres.

Follow up: Some weeks after the initial work-up the patient became hypothyroid, with increase in TSH levels and thyroid size. Thyroxine treatment was initiated.

Prevalence of extrathyroidal congenital anomalies associated with congenital hypothyroidism(CH)

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A high frequency of extrathyroidal anomalies has been reported in infants with CH. There are many reports about CH and congenital anomaly, they say there is a correlation between CH and congenital anomaly, considerably more common than in the general population. The aim of this study was to analyse prevalence of congenital anomalies in CH and compare with that of general population. We reviewed clinical data in 486 patients in Soonchunhyang University Hospital, in 2003-2008. Clinical characteristics of the 486 patients show 139(28.6%) dysmorphogenesis patients, 232(47.7%) hypoplasia patients, 19(3.9%) aplasia patients, 77(15.8%) ectopic thyroid patients. Most of them are identified through neonatal screening test. Only 10 patients(2.05%) have congenital anomalies. Compared with overall congenital anomaly prevalence(3%), it is lower than general population. Among them, 2 patients have polydactyly, 1 inward curving of 2nd toe, 2 patients have VSD, 1 patient has cleft palate, 1 ptosis, 1 shawl scrotum, 1 right ear lobe anomaly, 1 pseudohypoparathyroidism, so most of them are minor anomalies. Incidence of cardiac anomalies in CH reported over 6% which is most frequent, but our study shows only 0.4% incidence. Male:female ratio is 3:7. 6 patients are CH due to hypoplasia, 2 patients are due to dysmorphogenesis, 2 has ectopic thyroid. We concluded that congenital anomaly prevalence in CH is not high, extraordinarily different from previous reports. So more study will be necessary.

Infants with primary Congenital Hypothyroidism (CH) can be born with low T4 and normal TSH values. CH with delayed TSH rise possibly due to dysfunctional pituitary thyroid axis of still unknown genetic defect

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Familial occurrence of congenital hypothyroidism with delayed TSH rise possibly due to dysfunctional pituitary thyroid axis of still unknown genetic defect

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Case: A 13 year old girl presented with a small palpable mass located anteriorly of the thyroid gland. This was present for some weeks, sometimes painful and increased in size. Hoarseness, nor any other sign or symptom of thyroid disease was present. At physical examination no pathological lymph nodes were detected. The left lobe of the thyroid gland was increased in size, firm and smooth, non-nodular at palpation. At ultrasound the small mass appeared to be a lymph node. The thyroid gland was diffusely enlarged. The left lobe showed an inhomogeneous pattern with many reflections, mimicking small microcalcifications. A small nodular structure was observed near the isthmus.

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Conclusion: This case report emphasizes the diagnostic difficulties in the interpretation of an ultrasound pattern suspect for microcalcifications in children with thyroid enlargement, either nodular of non-nodular. Fine needle aspiration has to be performed even in presence of suggestive antibody titres.

Follow up: Some weeks after the initial work-up the patient became hypothyroid, with increase in TSH levels and thyroid size. Thyroxine treatment was initiated.
The two full-term and otherwise low risk siblings, had delayed TSH rise, which may have been the result of hypersensitivity of pituitary TSH secretion cells to thyroid hormone which suppress TSH in normal/subnormal T4. This is supported by the fact that both siblings always showed inappropriate TSH during follow-up measurements, whilst the levels of T4, FT4 and FT3 always remained within the normal range. The administered thyroid hormone dose had never been exceeded. It is likely that the same unknown genetic defect underlies both abnormalities in morphogenesis and function of the pituitary - thyroid axis.

**P2-d2-576 Thyroid 2**

**Neurophysiologic evaluation and intellectual outcome of children with congenital hypothyroidism**

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Thyroid hormones are essential for normal brain development for a critical period of time beginning before birth and extending through the first 2-3 years of life. Screening programmes for the detection of congenital hypothyroidism (CH) facilitating early diagnosis and treatment, have resulted in significant improvement of neurocognitive outcomes. For the purpose of detecting possible complications of the central and peripheral nervous system in patients with CH, 29 children aged 4-15.08 years (7.26±5.36 years) diagnosed early (44±34.7 days) in their infancy enrolled in the present study. Neurophysiologic evaluation consisting of visual (VEP), brainstem auditory (BAEP), and somatosensory (SEP) evoked potentials were performed along with cognitive assessment. Abnormal evoked potentials were detected in 2 patients (6.89%). VEP, BAEP, and SEP latencies were mild delayed in patients with more severe hypothyroidism (T4 levels at diagnosis ≤5µg/dl), in patients treated during the first 2-3 years of life. Screening programmes for the detection of congenital hypothyroidism (CH) identified by newborn screening, but IQ results vary depending on treatment and social characteristics.

**P2-d2-578 Thyroid 2**

**High dose versus low dose of L-(T4) for treatment of athyreotic newborns**

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Favorable outcome is typically described in follow-up studies of children with congenital hypothyroidism (CH) identified by newborn screening, but IQ results vary depending on treatment and social characteristics. For the purpose of detecting possible complications of the central and peripheral nervous system in patients with CH, 29 children aged 4-15.08 years (7.26±5.36 years) diagnosed early (44±34.7 days) in their infancy enrolled in the present study. Neurophysiologic evaluation consisting of visual (VEP), brainstem auditory (BAEP), and somatosensory (SEP) evoked potentials were performed along with cognitive assessment. Abnormal evoked potentials were detected in 2 patients (6.89%). VEP, BAEP, and SEP latencies were mild delayed in patients with more severe hypothyroidism (T4 levels at diagnosis ≤5µg/dl), in patients treated during the first 2-3 years of life. Screening programmes for the detection of congenital hypothyroidism (CH) identified by newborn screening, but IQ results vary depending on treatment and social characteristics.
Neonatal hyperthyroidism is a rare disease (1:50000 infants) and maternal Graves’ disease is its leading cause due to transplacental passage of maternal thyroid stimulating immunoglobulins (TSI). FR is a caucasian male. His mother is a 35 years old woman affected by Graves’ disease that required a total thyroidectomy and bilateral neck dissection. This diagnosis was definitely confirmed by histopathology after surgery. Autoantibodies may continue to be produced and even increase after surgical excision of the gland but they should be decreased to the normal range within six months. Nevertheless data of Graves’ disease should always alert the gynaecological and paediatric team in order to manage the neonatal hyperthyroidism as soon as possible and to prevent the onset of the potential risk of thyrotoxicosis: newborn should be carefully monitored and thyroid function tests and TSI titre should be performed within the 2nd day of life.

We aimed to assess the presenting complaints, clinical courses and outcomes of the children and adolescents with thyroiditis admitted in Dokuz Eylul University Medical Faculty Department of Pediatric Endocrinology between 1998 and 2008. A total of 145 patients (85.5% girls) with autoimmune thyroiditis were enrolled to the study. The cases, mean age of whom was 12.243.68, were followed for 3.825.50 years. The medical history, presenting complaints, physical examination findings at the time of presentation, ultrasonographic findings, (if performed) fine needle aspiration findings, comorbidities, the free T3, free T4, TSH, Anti TG, and Anti TPO levels, and treatment doses and durations of all patients were recorded. At the time of presentation, 41% of the cases were euthyroid, 11.7% hyperthyroid, and 8.7% hypothyroid. Compensatory hypothyroidism (subclinical hyperthyroidism) was present in 36.8% of the patients. At the time of diagnosis, ATPO and ATG antibodies were found to be positive in 81.4% and 77.9% of the cases, respectively. Ultrasonographic appearance consistent with thyroiditis were present in 92% of the patients. The 39.3% of the patients presented with goiter. Goiter was found in 64.1% of the patients with the physical examination at the time of presentation. The majority of the patients who were ultimately diagnosed with Hashimoto thyroiditis was euthyroid at the time of presentation. An increase in number of the patients with thyroiditis in recent years stands out when the distribution of the patients according to year was examined. Furthermore, it should also be considered that the frequency of autoimmune diseases has increased worldwide along with civilization and modernization.
Does thiocyanate overload play a role in the etiology of goiter in Isfahan, an iodine replenished area?

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Background: Despite long standing iodine supplementation in Iran the prevalence of goiter remains high in some areas. In the present study we investigated the possible role of thiocyanate (SCN) as a goitrogen in the etiology of goiter in Isfahan, Iran.

Methods: 2331 schoolchildren (6-13 year-old) were selected by multi stage random sampling. Thyroid size was estimated in each child by inspection and palpation. Urinary iodine concentration (UIC) and urinary thiocyanate (USCN) were measured.

Results: Overall, 32.9% of 2331 students had goiter. The median UIC was 19.55µg/dl. The mean ± SD of USCN in goitrous and nongoitrous subjects was 0.42± 0.28 mg/dl and 0.41± 0.32 mg/dl respectively (p=0.15). USCN level in goitrous and nongoitrous boys was 0.41 ± 0.32 mg/dl and 0.43 ± 0.37 mg/dl respectively (p=0.29). USCN level in goitrous and nongoitrous girls was 0.43 ± 0.26 mg/dl and 0.40 ± 0.28 mg/dl respectively (p=0.30).

Conclusion: In the studied population, thiocyanate overload does not play a role in high prevalence of goiter. We suggest the role of other goitrogenic factors should be investigated in this region.

Infantile hepatic hemangioma: A rare cause of severe hypothyroidism

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Congenital hypothyroidism is relatively common (incidence: 1/4000 newborns).

Etiologies include: thyroid dysgenesis (75%), dyshormonogenesis (10%), hypothyalmatic-pituitary deficiencies (10%), transient hypothyroidism (10%).

Hepatic haemangiomias (HHE) are the most common tumors in infancy (prevalence: 5-10%). They are benign endothelial cell neoplasms that exhibit rapid postnatal growth.

The HHE can be associated with significant morbidity: congestive heart failure, medically resistant hypothyroidism and abdominal compartment syndrome. The best explanation for hypothyroidism is an accelerated rate of inactivation of thyroid hormone by high type 3 iodothyronine deiodinase in the tumor mass, exceeding the synthetic capacity of the infant’s thyroid.

We observed 6 patients with HHE in the period 1999-2007: 2 of them showed hypothyroidism.

Case 1: female, observed at 1 month of age. At admission, physical examination was remarkable for jaundice, hepatomegaly, heart failure and multiple little cutaneous angiomas of the neck and lower limbs. Hypothyroidism was evident. We started L-thyroxin and treated HHE at first by interferon, then by somatostatin.

Case 2: 7 months old male, observed for hypothyroidism. Physical examination showed increased abdominal distension, umbilical hernia, hepatomegaly, small cutaneous angiomas of the left thigh, heart systolic murmur. Later, cardiac dysfunction worsened and consumptive hypothyroidism became more evident. Therefore partial embolization was performed and clinical conditions improved. L-thyroxin therapy was gradually reduced and stopped at the age of 2 years. We conclude that periodical screening of thyroid function is necessary in infants with diffuse and multifocal angiomas (especially HHE), while, if consumptive hypothyroidism is revealed, a vascular tumor should be searched.
CARBIMAZOLE was introduced at a low posology in the beginning because hyperthyroidism, such as tachycardia and ventricular dilatation without cardiac insufficiency, but no goiter but was otherwise asymptomatic. Her TSH was initially elevated (9.3) and FT4 normal. Her TFTs normalised within 2 months. 5 months later she became biochemically hyperthyroid (TSH 0.01, FT4 22.4) but remained clinically euthyroid. 2 months following this she became biochemically hypothyroid (TSH 182, FT4 less than 5.1) but her TFTs returned to normal within 2 months without treatment. In conclusion, autoimmune thyroiditis can result in a variety of rapidly changing serum TFTs. We suggest frequent monitoring of children with positive thyroid antibodies to decide on the correct line of management. The frequency of biochemical monitoring is an area for further research.

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Background: Although thyroid ultrasound is a valuable study for the diagnosis and follow-up of patients with Hashimoto’s thyroiditis (HT), classical sonographic findings are not always present at the initial work-up. Objective: to calculate the time needed for the 50% of children with HT and a normal ultrasound at diagnosis to develop an abnormal one.

Materials and Methods: Hundred and five children (23 male and 82 female) with HT and mean age 9.4±2.9 years were studied. Follow-up examination consisted of periodic (three months interval for the first year and twice yearly thereafter) clinical examination, measurements of TSH and FT4 levels, and thyroid ultrasound. The median duration of follow-up was 18 months (range: 6-61 months). Kaplan-Meier statistical method of estimating “survival” and log rank test was used to calculate the time needed for the 50% of children with normal ultrasound to have thyroid abnormalities at thyroid ultrasound and to compare “alteration” curves between groups.

Results: The time needed for the 50% of the children to demonstrate an abnormal sonographic pattern of the thyroid gland is 8 months. Important factors that accelerate the appearance of sonographic changes are goiter (P = 0.023), hypothyroidism (P = 0.0255), and seropositivity for both thyroid peroxidase (anti-TPO) and thyroglobulin autoantibodies (anti-Tg) (P = 0.0005).

Conclusion: sonographic findings such as diffusely abnormal thyroid gland, heterogeneous and hypoechoic pattern, diaphragms and fibrosis, fine micro-nodular appearance and focal thyroiditis may be absent for more than four years in children with AITD.

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The concentrations of thyroid hormone in preterm infants are lower than that of term infants. There is an obtunded thyrotropin peak immediately after birth while TSH remains below 20 mIU/L the cut off point for congenital hypothyroidism in the period of low T4. This period is generally referred as transient hypothyroxinemia of the preterm infant. Apart from hypothyroxinemia specific for prematurity other abnormalities of thyroid function can occur. To examine the short term clinical effects of thyroid hormone replacement therapy in infants with a gestational age of 24-33 week with a Free T4 < 0.8 ng/dl. A total of 37 infants were enrolled. 20 of the infants received 8 ug/kg L-thyroxine therapy. 17 infants with the same agap scores, birth weight, sex ratio, prenatal treatment, mode of delivery, or the incidence of respiratory distress syndrome but with a TSH< 10 and Free T4 > 0.8 ng/dl served as the control group for the longitudinal follow up of height, weight and head circumference. The blood was drawn at a mean age of 12,4±8.8 days. There was no significant difference in between the groups according to weight, height and head circumference in the follow up period up to 12 months except weight of the control group was significantly different on the first month of therapy (1,89±0,38 vs. 2,32±0,45, p=0,025) and height was significantly different on the 6th month (60,2±5,6 vs. 63,3±4,3, p=0,03) Infants with a Free T4 level < 0.8 ng/dl did benefit from thyroid hormone replacement therapy as shown with the catch up of weight, height and head circumference with respect to the control group but we still need a control group with Free T4< 0.8 ng/dl without medication.

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High initial dose of L-thyroxine is suggested to normalize serum thyroid hormone levels faster, improving the outcome especially in severe cases with congenital hypothyroidism (CH). However lower doses may be sufficient in milder cases. Aim was to analyze the effect of initial dose of L-thyroxine on serum hormone levels in cases with CH of varying severity. 128 neonate/infants with CH were categorized into 4 groups of severity according to initial serum FT4 levels: (1) borderline (FT4<12 µg/dL; n=20) (2) mild (FT4: 8-12
The ability to also replace the prepubertal estrogens in girls with Turner’s Syndrome is archaic in girls with Turner’s Syndrome (JCEM 81;4095). However, the possibility to mimic the spontaneous levels as well as the diurnal pattern of serum estradiol seen in spontaneous early puberty and induce thelarche nocturnally is possible to mimic the estradiol levels seen in healthy prepubertal and peripubertal in girls, but induce breast development of estradiol patches applied nocturnally mimic the estradiol levels seen in healthy prepubertal and peripubertal in girls, but induce breast development. Four girls with Turner’s Syndrome have started their replacement therapy with ultra low doses aiming estradiol concentration seen in healthy prepubertal girls without breast development. Ages ranged: 11.6-13.1 years and all girls were prepubertal at start with increased s-FSH. A transdermal matrix patch of estradiol (Evorel®, Jansen-Cilag, 25 µg/24 hours) was cut into 1/12-1/14 of a patch, (1.8-2.1 µg parts), corresponding to 0.033-0.042 µg estradiol/kg girl and attached to the buttock nocturnally. Blood samples for estradiol measurements were drawn in the morning before the patch was removed in order to obtain the highest 24 hour serum estradiol level of the treatment. Serum estradiol was measured by extraction RIA. The detection limit was 4 pmol/L and the interassay CV at 6 pmol/L was 20% (EJE 158;117). The morning serum estradiol concentrations with the patch attachment ranged <4-14 pmol/L, median 8 pmol/L. The upper limit of the prepubertal range of morning estradiol in healthy girls is 11 pmol/L. Three of the four girls developed breast stage 2 after 2-6 month of treatment. We conclude that 0.04µg/kg of estradiol patches applied nocturnally mimic the estradiol levels seen in healthy prepubertal and peripubertal in girls, but induce breast development in Turner’s Syndrome. The dose and patch application/duration to remain prepubertal need to be further elucidated.

P2-d2-591 Turner Syndrome
Inhibins A, B and anti-mullerian hormone as markers of ovarian reserve in girls with Turner’s syndrome
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Introduction: Spontaneous fertility is rare among Turner’s syndrome patients. Karyotype 45 XO, mosaicism with XY & Xq deletions has been associated with hypoplastic ovaries & uterus whereas women with 46 XX mosiacism, terminal p deletions or ring X chromosome have been shown to be fertile. Anti-Mullerian hormone (AMH) has been found to positively correlate with ovarian function.
Objective: 1). To explore the relation between AMH & other markers of ovarian function like uterus & ovaries visualized by pelvic sonogram and gonadotropins
Methods: Retrospective chart review of all patients with Turner’s syndrome in our clinic.
Results: There were 14 patients mean age 13.4 +/- 4.6 years & mean age at diagnosis 7.9 +/- 4.5 years. Two groups were identified: group 1 with a karyotype with poor probability of fertility and group 2 with fair probability of fertility. In group 1: 4 patients had 45XO, 1 had 45XO/46XY, 1 had Xq deletion and 3 had mosaicism 45 XO/46Xr (X). In group 2: 2 had terminal Xp deletion & 2 had 45XO/46XX. Regardless of karyotype, all had undetectable inhibin B. The group with fair probability of fertility had detectable AMH and measurable inhibin A whereas the group with poor fertility probability had undetectable AMH and inhibin A. Pelvic sonogram and gonadotropin levels were consistent with karyotype.
Conclusions: Pelvic sonogram findings & gonadotropins are good markers of ovarian function & correlated well with karyotype. AMH & inhibit A need to be explored further as markers of ovarian reserve and hence cryopreservation in Turner’s syndrome.

P2-d2-592 Turner Syndrome
Ultra-low dose of estradiol patch to girls with Turner syndrome result in prepubertal and peripubertal levels of morning estradiol
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By cutting a transdermal estradiol matrix patch and attaching a part of it, corresponding to 0.08-0.12 µg estradiol/kg body weight, to the buttock nocturnally it is possible to mimic the spontaneous levels as well as the diurnal pattern of serum estradiol seen in spontaneous early puberty and induce thelarche in girls with Turner Syndrome (JCEM 81;4095). However, the possibility to also replace the prepubertal estrogens in girls with Turner Syndrome is an approach that that is very attractive from a physiological view. Prepubertal estrogen replacement therapy may have effect on uterus and breast development and promote longitudinal growth and improve the outcome of pubertal replacement therapy. Four girls with Turner’s Syndrome have started their replacement therapy with ultra low doses aiming estradiol concentration seen in healthy prepubertal girls without breast development. Ages ranged: 11.6-13.1 years and all girls were prepubertal at start with increased s-FSH. A transdermal matrix patch of estradiol (Evorel®, Jansen-Cilag, 25 µg/24 hours) was cut into 1/12-1/14 of a patch, (1.8-2.1 µg parts), corresponding to 0.033-0.042 µg estradiol/kg girl and attached to the buttock nocturnally. Blood samples for estradiol measurements were drawn in the morning before the patch was removed in order to obtain the highest 24 hour serum estradiol level of the treatment. Serum estradiol was measured by extraction RIA. The detection limit was 4 pmol/L and the interassay CV at 6 pmol/L was 20% (EJE 158;117). The morning serum estradiol concentrations with the patch attachment ranged <4-14 pmol/L, median 8 pmol/L. The upper limit of the prepubertal range of morning estradiol in healthy girls is 11 pmol/L. Three of the four girls developed breast stage 2 after 2-6 month of treatment. We conclude that 0.04µg/kg of estradiol patches applied nocturnally mimic the estradiol levels seen in healthy prepubertal and peripubertal in girls, but induce breast development in Turner’s Syndrome. The dose and patch application/duration to remain prepubertal need to be further elucidated.

P2-d2-593 Turner Syndrome
Liver anomalies in 75 patients with Turner syndrome (TS): Follow-up until the young adult age
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Raised liver enzymes, cholestasis and higher risk of hepatopathy such as cirrhosis have been reported in TS. Aim of the study was to evaluate in TS the liver function and the prevalence of steatosis and the influence of GH-therapy, estrogens, autoimmunity, age, obesity and insulin resistance.
Methods A group of 75 patients with TS, that reached final height (FH) with GH therapy at high doses (0.33 mg/Kg/week), were yearly investigated for hepatic function (AST, ALT, γGT, ALP), serum lipids, insulin sensitivity, βcell function, autoantibodies and BMI with a follow-up of 12.8 +/- 4.8 yrs. Abdominal ultrasound was performed in 42/75 patients at least once, mostly in patients with raised liver enzymes. In 4 pts submitted to liver biopsy, the fatty liver was confirmed with NASH.
Results 12/75 patients presented persistently raised liver enzymes. Fatty liver was found in 67 % of TS patients with some elevation of liver enzymes. BMI distribution was similar to the GP (5.3% >97° pc). AST, ALT and γGT levels were influenced by age, BMI, 45X and X structural anomalies (X-SA) karyotype, but not by GH-therapy and estrogens. TS pts with high ALT, AST or γGT levels had a high RR to develop steatosis (respectively 2.5, 2.1 and 1.9 times more than patients without). Patients with 45X and X-SA seemed to risk steatosis more. Pts with spontaneous ovarian activity seemed to risk steatosis less. Serum lipids and insulin resistance showed no influence on risk of fatty liver. Autoimmunity showed no influence on liver function and steatosis. Conclusions Most of the pts showed a mild and transient liver dysfunction. The abnormal liver function correlated with age, BMI, karyotype. Fatty liver correlated with raised ALT, AST, γGT and 45X or X-SA, not with BMI. GH-therapy and estrogens seemed to lower fatty liver risk. Our study supports the hypothesis of genetic origin of liver steatosis in TS.