Increasing evidence points to the role of hypoadiponectinemia on the insulin resistance in obesity. This study aimed 1) to investigate the relationship between serum adiponectin level and metabolic parameters and other adipokines (leptin, resistin and visfatin) 2) to clarify the usefulness of serum adiponectin level as a diagnostic marker of metabolic syndrome (MS) in obese children. A total of 239 obese (age, sex specific BMI>85P) schoolchildren aged 11.5±1.7 (9 to 15 years) in Seoul, Korea were included. Anthropometric variables (height, weight, waist circumference, fat percent), fasting insulin, glucose, triglyceride and HDL-cholesterol were measured. Serum adiponectin, leptin and resistin were measured by ELISA, and visfatin was measured by ELIA. We defined pediatric MS based on the modified Adult Treatment Panel III report criteria. Adiponectin level was inversely related to BMI (r=-0.01), waist circumference (r<0.01), diastolic blood pressure (r=0.05), fasting serum insulin (r=0.01), HOMA-IR (r=0.01), triglyceride (r<0.01), and positively related to HDL-cholesterol (r>0.01). Adiponectin was not related to total fat percent, leptin and visfatin level. In multiple stepwise regression, adiponectin was significantly related to triglycerides (r<0.01) and waist circumference (r<0.01) independent of age, gender and BMI. Adiponectin level was lower in children with MS compared to non-MS (7.1±2.3 vs 7.7±3.1 in boys, 6.6±2.5 vs 8.5±3.3 in girls, P<0.01). There were significant differences in BMI, waist circumference, fasting serum insulin, HOMA-IR, triglycerides levels, and the prevalence of MS among the three groups divided according to the aipontin levels. Hypoadiponectinemia was highly associated with MS in obese children. Evaluation of serum adiponectin level might contribute to an early detection for obese children with MS.

<table>
<thead>
<tr>
<th>Tertile I</th>
<th>(&lt;6.2), n=83</th>
<th>Tertile II</th>
<th>(6.2~8.6), n=81</th>
<th>Tertile III</th>
<th>(&gt;8.6), n=75</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>4.6±1.1</td>
<td>7.4±0.6</td>
<td>10.9±2.3</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>27.6 ± 3.1</td>
<td>27.0 ± 2.8</td>
<td>26.4 ± 2.6</td>
<td>0.04</td>
<td></td>
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</tr>
<tr>
<td>HOMA-IR</td>
<td>5.3 ± 4.8</td>
<td>4.5 ± 2.7</td>
<td>3.9 ± 2.4</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>172.1 ± 87.9</td>
<td>153.2 ± 74.6</td>
<td>133.3 ± 60.8</td>
<td>0.006</td>
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<tr>
<td>Prevalence of MS (%)</td>
<td>54.2</td>
<td>50.6</td>
<td>29.3</td>
<td>0.002</td>
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</tbody>
</table>

**P2-d1-436 Obesity and Fat 1**

**Clinical, endocrine, metabolic, and polysomnographic findings in 37 adolescents with polycystic ovarian syndrome**

Gideon de Sousa; Bernhard Schlüter; Dirk Buschatz; Eckard Trottzsch; Werner Andler; Thomas Reinehr

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**Introduction:** The incidence of obstructive sleep apnoea syndrome (OSAS) is increased in adults with polycystic ovarian syndrome (PCOS). Diagnosing and treating OSAS is of great importance, as OSAS represents a cardiovascular risk factor, which contributes to cardiovascular morbidity and mortality. Data on the incidence of OSAS in adolescents with PCOS are limited.

**Methods:** We recorded the clinical (age, height, weight, body mass index (BMI), standard deviation score of body mass index (SDS-BMI)), endocrine (serum levels of testosterone, fasting insulin), and metabolic (fasting serum levels of glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) data of 37 adolescents with PCOS. Twenty-two patients had a history pointing towards sleep-related breathing disorders and underwent overnight 12-channel polysomnography. All patients underwent an oral glucose tolerance-test (OGTT). Insulin resistance was calculated using the HOMA-index (resistance (HOMA) = (insulin [mU/l] x glucose [mmol/l]) / 22.5).

**Results:** Mean age of the patients was 15.24 years (± 1.31), mean BMI 30.92 kg/m2 (± 6.68), and mean SDS-BMI 2.11 (± 1.19). Six patients were normal weight, 5 overweight, 7 obese, and 19 extremely obese. Polysomnography revealed no abnormalities in the 22 examined patients. Mean testosterone level was 1.90 nmol/l (± 0.48; normal range < 1 nmol/l). Thirty-six girls had elevated testosterone levels, the girl with the normal testosterone level was already being treated. Five patients demonstrated impaired glucose tolerance in the OGTT. Eighteen girls had pathological insulin resistance. Sixteen patients showed no disturbance of glucose metabolism. We found decreased HDL-cholesterol levels in 6 patients, elevated LDL-cholesterol levels in 9 patients, elevated total cholesterol levels in 6 patients, and elevated triglycerides in 34 patients. Three girls had normal lipids.

**Conclusion:** OSAS does not seem to be common in adolescents with PCOS, whereas disturbances of glucose- and lipid metabolism are frequently observed in this group of patients.

**P2-d1-437 Obesity and Fat 1**

**Nitric oxide production in Peripheral Blood Mononuclear Cells (PBMC) measured in prepubertal and pubertal children**

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**Background:** Nitric oxide (NO) produced from amino acid L-arginine by the endothelial NO synthase is a potent vasodilator. Previous study showed that endothelial vasodilation was better in pubertal children compared with prepubertal. Based on that data we hypothesized that we can find a difference in NO production between pre-and pubertal children.

**Objective:** This study was design to examine the relationship btw. NO production in PBMC in pre- and pubertal children by measuring Nitrate NO3- and Nitrite NO2- byproducts using Griess reagent method.

**Design/Methods:** 2 groups were established: prepubertal (ave. age 11.29; n=9, 3f, 6m) and pubertal (ave. age 13.15; n=20, 9f, 11m). PBMC were extracted from blood and purified with phosphate buffer. Index of NO was predicted by measuring final byproducts: NO2- and NO3-. We converted NO3- to NO2- by nitrate reductase. Conversion reaction of NO2- and Griess reagents produces stable purple color azo end product, which was quantified by colorimetric analytical techniques. Ht, Wt, waist circ(WC), BMI, fasting lipid profile, glucose, insulin and DHEAS levels were measured.

**Results:** There were no differences in age, BMI, WC, cholesterol, HDL, LDL, glucose and insulin within the groups. There were no sign. differences in index of NO production between pre- and pubertal groups. Index of NO production negatively correlated with BMI (r = -0.51; p<0.05) (Figure 1), and WC (r = -0.49; p<0.05) (Figure 2).
Conclusion: No difference in NO production between 2 groups in our study can be secondary to the fact that PBMC were extracted and washed out before experiment that could eliminate the influence of pubertal sex steroids on NO production in these cells. Risk factors for atherosclerosis like obesity and visceral obesity are associated with endothelial dysfunction in adults. In our study we are for the first time found significant negative correlation between index of NO production in PBMC and risk factors for endothelial dysfunction, as obesity and specifically visceral obesity, measured by WC.

**P2-d1-438** Obesity and Fat 1
Impact of body mass index and waist circumference on coronary artery disease risk factors in Iranian children and adolescents
Peymaneh Sarkhail; Farzad Hadaegh; Mojgan Padyab; Feridoun Azizi; Peymaneh Sarkhail
Prevention of Metabolic Disorders Research Center, Endocrinology and Metabolism, Tehran, Islamic Republic of Iran

Objectives: To define whether combined body mass index (BMI) and waist circumference (WC) could predict coronary artery disease (CAD) risks better than either of them independently in Iranian children and adolescents.

Methods: Subjects included 1937 girls and 1742 boys, 3 to 18 years old. BMI and WC were used as continuous variables to predict risk factors. After categorization of indices, CAD risks were compared among different BMI groups, in each WC category.

Results: BMI and WC could predict different CAD risks as continuous variables in the regression model similarly (3.3% to 14% and 3.5% to 12.3% for BMI and WC respectively). When BMI and WC were included in the model, the odds ratio (OR) for I-SD change in BMI was significant only for high LDL cholesterol (OR=1.39) and in WC for high fasting plasma glucose, high triglycerides, and low HDL cholesterol (OR=1.62, 1.95, and 1.4 respectively). After categorization parameters, only in normal BMI, high WC subjects had greater mean and OR of metabolic syndrome components than low WC.

Conclusion: WC per se had more effect on metabolic syndrome components, and in clinical settings adding WC to a given BMI could predict CAD risks in normal BMI subjects only.

**P2-d1-439** Obesity and Fat 1
Association of cardiovascular risk factors in adolescents with different energy expenditure levels
Luís Paulo Mascarenhas¹; Antonio Stabelini Neto¹; Anderson Z. Ulbrich²; Rodrigo Bozza²; Italo Q. A. Vasconcelos³; Margaret C. S. Boguszewski³
¹Universidade Federal do Paraná, Unidade de Pediatria Endorina, Curitiba, Brazil; ²Universidade Federal do Paraná, CEPEE, Curitiba, Brazil

The contemporaneous style of live is highly associated with sedentary behavior and may be associated with the development of cardiovascular diseases in adolescents. Identify the different energy expenditure levels of daily activity and prevent possible factors connected with cardiovascualrs risks are crucial. Objective: To verify the predisposition of the cardiovascular disease risk factors in adolescents with different energy expenditure levels.

Methodology: 66 males and 116 females were selected, with ages between 12 to 16 years old. The daily energy expenditure was obtained by Bouchard questionnaire. For group composition, the sample was separated through quartiles of energy expenditure (Kcal/kg/day); sedentary (GS), moderately active (GM) and active (GA). The concentrations of total cholesterol (TC), HDL-C and triglycerides (TG) were measured by the enzymatic-colorimeter method. LDL-C was calculated by Friedewald equation. ANOVA’s one-way was used for statistical analyses, adopting p<0.05.

Results: For males, significant differences were found among the groups in the variable TC (mg/dl), being GA (121.56 ± 19.15) different from GM (142.70 ± 27.65) and GS (145.63 ± 36.54), as well GM differed of GS (F = 3.70 and p=0.03). For the TG (mg/dl), GA (65.69 ± 18.95) differed from GM (82.25 ± 33.73) and GS (97.44 ± 45.95), as well GM differed of GS (F=3.40 and p=0.04). For girls, no significant differences were found in function of the daily energy expenditure.

Conclusion: The more active males presented less total cholesterol and triglycerides concentrations than their pairs moderately active and sedentary. Apparently in girls the association of daily energy expenditure and cardiovascular risk factor is weak.

**P2-d1-440** Obesity and Fat 1
Hepatosteatosis association with impaired glucose tolerance and hyperinsulinism in adolescents
Tolga Fier
Afyon Kocatepe University, Pediatric Endocrinology, Afyonkarahisar, Turkey

Aim: We aimed to show hepatosteatosis in obese adolescents in relation to impaired glucose tolerance and hyperinsulinism.

Material and Methods: A two hours oral glucose tolerance test and abdominal ultrasonography were performed for the 98 obese adolescents (56 females, 42 males) whose body mass indexes were above the 95. percentile.

Results: The mean age was 13±4 years. Hepatosteatosis was detected in 36 (36.7%) of the obese adolescents. Impaired glucose tolerance during fasting was found in 19 (19,3%) and hyperinsulinemia was found in 17 (17,3%) of them. Hypertriglyceridemia was found in 12 (12,2%) and hypercholesterolemia was found in 9 (9,1%) of them. All cases had normal systolic and diastolic blood pressure.

Conclusion: All the cases with hyperinsulinemia, impaired glucose tolerance and dyslipidemia had also fatty liver. There was a direct relationship between the degree of obesity and the prevalence of fatty liver. Pediatric hepatosteatosis is associated with obesity, impaired glucose tolerance, insulin resistance and dyslipidemia and may be a component of metabolic syndrome.

**P2-d1-441** Obesity and Fat 1
Risk factors for overweight and obesity among Bulgarian children and adolescents, aged 6-18 years
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¹University Hospital, Clinic of Pediatric Endocrinology, Varna, Bulgaria; ²Military Hospital, Dept. of Internal Medicine, Varna, Bulgaria; ³Varna Medical University, Dept. of Hygiene and Ecology, Varna, Bulgaria

Childhood obesity is a complex condition influenced by a variety of genetic and environmental factors. It has a tendency to track into adulthood with increased metabolic and cardiovascular risk. Our aim was to identify the relationship between childhood overweight/obesity and children’s eating and exercise habits, family/parental status and some further characteristics. A cross-sectional study of an urban sample of 3810 healthy children/adolescents (53.9% boys), aged 6-18 years, was conducted in 2006/2007. Body weight, height and waist circumference (WC) were measured using standard procedures, BMI was calculated. Weight status (normal weight and overweight/obesity) was estimated using the IOTF reference. A questionnaire was used to obtain data about family history, breast-feeding, parental weight status, children’s eating and physical behavior. The prevalence of overweight/obesity was 28.7% for the whole studied group with no significant gender differences. The younger children were more overweight/obese (32.2% for 6-11y, 25.9% for 12-18y).
Obesity is increasing universally with most pronounced tendencies among children. The present work aims at assessing the trends of obesity/overweight (OW) among prepubertal children over a period of 18 years. Three urban population-based datasets are analyzed. The first (1st gr.) is a subset of 1162 students, a part of a 1980-82 birth cohort followed from birth to final height, and with present BMI (kg/m2) records at 9 years of age. The second one (2nd gr.) consists of 247 students aged 9 and examined in 2001 as a part of a larger obesity project. The third one (3rd gr., n=304) is studied in 2006-2007 as a part of the elaboration of national waist circumference reference. All datasets contain information about weight and height of the parents and television (TV) viewing. Obesity/OW was defined according to the internationally accepted IOTF reference. Obesity prevalence increases significantly among boys - 3.2% (1st gr.), 9.2% (2nd gr.) and 10.6% (3rd gr.), p<0.0001 for trend. Among girls, obesity rises sharply in 3rd gr. (4.9% vs. 4.3% vs. 10.4%, p=0.027). The relative share of OW-only boys increases during the last years (14.6%; 10.0%; 19.4%, 2nd vs. 3rd gr. p=0.03) while for OW-only girls the prevalence shows sustained rise with time (14.3% vs. 17.1% vs. 24.3%, p=0.004). The mean BMI of all boys (17.0±2.4 vs. 17.1±2.9 vs. 18.3±3.1, p=0.001) and of all girls (17.2±2.9 vs. 17.0±2.9 vs. 18.5±3.3, p=0.001) also increase with time. Interestingly, there is a sustained trend towards decrease of mothers’ BMI with time in both boys (p=0.004) and girls (p=0.001), while the BMI of girls’ fathers is increasing (p=0.001). TV viewing diminishes significantly in 3rd gr., who spend considerable time in front of computers. The trend towards obesity/OW increase among prepubertal Bulgarian children has reached epidemic proportions during the last 6 years which is calling for urgent measures.

Obesity and Fat 1

Hyperthyrotoxine in prepubertal children (not an insulin resistance related mechanism)

Elena Falaschin; Federico Verzegnassi; Eva Da Dalt; Stefania Bassanese; Alessia Saccari; Giorgio Tonini

IRCCS Burlo Garofolo, Department of Pediatrics, Trieste, Italy

Background: Recent evidences suggest hyperthyrotoxine (HTT) to be more frequent in obese children than in healthy controls. The mechanism affecting TSH increase is still not well understood. Some authors suggest a role of leptin in TRH release, others an insulin resistance (IR) independent effect.

Subjects and Methods: We investigated 147 obese children (Cole index > 2DS) (age range 8.28-13.69yrs) for TSH, FT3, FT4, TPO and TG abs, thyroid sonography, HOMA, and leptin.

Results: (expressed in M±SD). We found HTT (TSH >4.2 mcU/ml) in 31.57% of HTT, 2.78±1.76 and in 30.08% of non HTT, 2.94±2.13. TSH was slightly higher in IR than in non IR (3.03±1.26 vs 2.90±1.60 mcU/ml) without statistical significance. Mean leptin value was higher in IR than in non IR children 19.14±8.539 vs 14.68±12.07 ng/ml (p=0.026).

Conclusions: Our experience suggest a role of obesity in HTT. Leptin could play a role, but high leptin, which is more frequent in IR subgroup, is also more frequent and higher in non HTT than in HTT. IR frequency is the same in the two groups and TSH is only slightly increased in IR obese. Our data therefore do not completely support both mechanisms. More investigations are necessary to better understand HTT in obese.

Obesity and Fat 1

The prevalence of thyroid test dysfunction in obese children and adolescence before and after weight reduction programs and their relations to other metabolic parameters

Shiomit Shalitin; Michael Yackobovitch-Gavan; Moshe Phillip

Jesse Z and Sara Lea Shafer Institute for Endocrin, National Center of Childhood Diabetes, Schneider C, Petah Tikva, Israel

Abnormalities in thyroid function were described in individuals with obesity. We evaluated the prevalence of hyperthyrotoxine in obese children and adolescents, and the relationship between changes in TSH levels and metabolic and hormonal parameters before and after weight reduction programs. Anthropometric, biochemical, metabolic and hormonal parameters were measured at baseline and at the end of the intervention in 207 obese participants aged 5-18 years who were enrolled into weight reduction programs. At baseline 46 participants (22.2%) had elevated TSH levels (≥4.0 mU/L). FT4 levels were within the normal range in all participants, without significant difference between the group with hyperthyrotoxine and that with normal TSH. Obese boys with hyperthyrotoxine had significantly elevated triglycerides levels compared to obese boys with normal thyroid functions (p=0.047). No significant differences in other anthropometric or laboratory parameters were found between the group with hyperthyrotoxine and the group with normal TSH. We found a significant positive correlation between baseline TSH level and triglyceride levels (r=0.261, p<0.001). Thirty (20 %) out of 147 participants who completed the intervention programs had elevated TSH levels. There were no significant differences in TSH level changes during the interventions in relation to changes in BMI-SDS. At the end of the interventions, comparison between the group with normalization of TSH and the group with hyperthyrotoxine did not find significant differences in change in anthropometric parameters. A significant positive correlation was found between TSH level at the end of the intervention and triglyceride levels (r=0.167, p=0.045), and a positive correlation between the decrease in TSH levels and decrease in waist circumference (r=0.291, p=0.013). The presence of elevated TSH levels with normal FT4 levels in obese children seems to be frequent and is correlated with higher triglyceride levels, raising the question of the necessity to treat the elevated TSH levels in obese children.

Obesity and Fat 1

Prevalence of dyslipidemia in Iranian children and its relationship with anthropometric indices (TLGS Study)

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Prevention of Metabolic Disorders Research Center, Endocrinology and Metabolism, Tehran, Islamic Republic of Iran

Objectives: Cardio-vascular diseases (CVD) is one of the most important causes of death in the world. It is shown atherosclerosis begins in childhood period and it is strongly related to serum cholesterol. In this study we try to show the prevalence of dyslipidemia in Iranian children and its relationship with anthropometric indices.

Method: 932 children 3-9 year old (485 female and 447 male) were enrolled...
in this cross sectional study. Firstly the frequency of hyperlipidaemia was determined according to NCEP-Peds cutoffs in 1992 and then age adjusted relationships with anthropometric indices were defined by Pearson correlation test. Finally the best predictor of high cholesterol (Chol), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), Non-HDL-C, Non-HDL-C/HDLC, Chol/ HDLC, TG/HDL-C, and low HDLC by logistic regression analysis were determined.

Results: The overall frequency of hypertriglyceridemia, hypercholesterolemia, high LDL-C, low HDLC among our children were 29.8%, 15.8%, 16%, and 18.3% respectively. Prevalence of high cholesterol and high LDL-C were significantly higher in girls than boys. (P<0.05) We found relationship between total cholesterol (r=0.12, P<0.001), LDL-C (r=0.12, P<0.001), TG (r=0.19, P<0.001), and HDL-C (r=-0.12, P<0.001) with waist to height ratio (WHIR). In logistic regression analysis also WHIR was the best predictor for hypercholesterolemia (OR=1.35, CI=1.13-1.61), high LDL-C (OR=1.36, CI=1.13-1.62), Non-HDL-C (OR=1.41, CI=1.15-1.73) with P-value less than 0.001. The OR of waist for high TG and high TG/HDL-C were 1.47 (CI=1.69-3.12) and 1.50 (CI=1.22-1.83), and for both high cholesterol/ HDL-C and high Non HDL-C/HDLC-C which were defined by BMI OR were 1.25(CI=1.04-1.51).

Conclusion: It seems the prevalence of dyslipidaemia in childhood period is significant. Measurement of anthropometric indices other than BMI and Waist circumference especially WHIR, could give useful information to predict hyperlipidaemia in children.

**P2-d1-446 Obesity and Fat 1**

**Characterization and heritability of predisposition to insulin resistance: Comparison of an obese with a normal child population**

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Insulin resistance, so as obesity, both conditions significantly associated, results from the interaction of genetic factors with environmental ones. This study aims at: 1) Characterizing the proportion of obese children predisposed to insulin resistance in comparison with a normal control child population 2) Comparing the heritability of predisposition to insulin resistance between both child populations.

**Materials:** 474 non obese children ; 600 obese children (BMI : 4.6 +/- 1.3 SD)

**Methods:** Index of insulin resistance : HOMAIR. Heritability estimates : variance components procedure through SOLAR software.

**Results:** Comparison of insulin resistance between control and obese children 

- Only 1.3 % of the obese is characterized by a HOMAIR less than the 10th percentile for the control children (insulin sensitive subjects) vs 53.8 % of the obese characterized by a HOMAIR more than the 90th percentile for the normal population. Same results are obtained when correcting HOMAIR for gender and age, but when correcting it for gender, age, + BMI (HOMAIR R GAB), 8 % (NS) of the obese are located under the 10th percentile for the control, vs 14.5 % (p < 0.001) of them (called predisposed to insulin resistance) located beyond the 90th percentile for the normal population. Heritability coefficient of HOMAIR GAB from fathers to sons is 1 (p = 0.0001) and from fathers to daughters is 0.94 (p = 0.000004), vs non significant from mothers to sons and daughters, while in the obese population respective coefficients vary from 0.16 to 0.27.

**Conclusions:** 1) gender, age (pubertal stage) and, over all, BMI being the most known environmental factors for insulin resistance, predisposition to insulin resistance accounts for a modest but significant (about 50 %) excess of obesity cases in a child population. 2) Insulin resistance is exclusively paternaly imprinted (IGF2- insulin genes ?) in a normal child population but this pattern is faded by specific genetic and epigenetic factors in an obese one.

**P2-d1-447 Obesity and Fat 1**

**Prevalence of insulin resistance and impaired glucose tolerance in obese children and adolescents**

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Obesity in children may lead to insulin resistance and impaired glucose tolerance. The aim of this study was to establish the prevalence of insulin resistance and impaired glucose tolerance (IGT) in a cohort of obese children and adolescents. The studied group included 88 patients (age range: 10 - 16 yrs) with a BMI greater than +1.5 SDS. Estimates of insulin resistance (HOMA-IR), insulin sensitivity (QUICKI) and pancreatic b-cell function (HOMA%B) were derived from fasting measurements. An oral glucose tolerance test (OGTT) was performed to determine the presence of IGT. Serum glucose was measured by the glucose oxidase enzymatic method (Beckman Synchro Linox-20) and serum insulin concentrations were determined by an immunometric assay with the Siemens Advia Centaur Insulin (IRI) assay. Insulin resistance (HOMA-IR>2) was detected in 72 (82%) patients; impaired insulin sensitivity (QUICKI<0.339) in 72 (82%). HOMA-IR and QUICKI were related to BMI-SDS (r = +0.36; p < 0.001 and r = -0.34; p < 0.001, resp.), but not to age. None of the patients had silent diabetes. IGT was present in 11 (13%) subjects. 6 patients had impaired fasting glucose; only 2 of them also had IGT. The table compares data of patients with IGT with those with normal GT. Patients with IGT had higher fasting insulin levels, a lower QUICKI and a higher HOMA-IR index. The HOMA%B index was not different between both groups, suggesting that IGT is associated with relatively preserved b-cell function.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>BMI (SDS)</th>
<th>Fasting glucose (mg/dl)</th>
<th>Fasting insulin (µU/ml)</th>
<th>QUICKI</th>
<th>HOMA-IR</th>
<th>HOMA-%B</th>
</tr>
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<td>IGT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>13.1</td>
<td>±1.6</td>
<td>2.9</td>
<td>9149</td>
<td>36217</td>
<td>0.289</td>
<td>8.3</td>
</tr>
<tr>
<td>Normal GT</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>13.5</td>
<td>±1.8</td>
<td>2.7</td>
<td>8748</td>
<td>20x10</td>
<td>0.317</td>
<td>4.4</td>
</tr>
</tbody>
</table>

*p<0.02; **p<0.005

We conclude that insulin resistance is highly prevalent in obese children and adolescents. Fasting glucose is not a useful screening tool for IGT in young patients. Indices derived from fasting glucose and insulin levels are reliable screening criteria in these patients for diagnosis of insulin resistance/sensitivity. An OGTT is required in all subjects at high risk to detect IGT.
than 2.7 ng/ml BP was kept in normal for age ranges. It was found that in obese individual without puberty deviation, BP is strongly associated with set of hormones: SBP = 0.92*IRI + 1.09*L + 0.14*C (R2 = 0.90, P = 0.0001); DBP = 0.65*IRI + 0.69*L + 0.07*C (R2 = 0.90, P = 0.0001). Evidences of association between arterial blood pressure components and set of hormones, were obtained. Our results may provide additional evidence that hypertension in obese adolescent boys is caused by hormonal factors, strongly associated with state of insulin resistance.

**Background:** Modifications of thyroid size and function (TF) have been reported in obese children (OC). A correlation between BMI and TSH has also been reported.

**Objective:** To investigate the prevalence of TF abnormalities and the effects of puberty and weight loss in a large number of OC. We also evaluated whether the TF abnormalities correlate with the degree of obesity and circulating lipids.

**Subjects And Methods:** 468 OC aged 3.7-17.9 years, 255 girls [116 Tanner stage (T) I and 139 T II-IV, and 213 boys, 139 T I and 74 T II-IV] and 62 normal weight children as controls (C). Obesity was defined by a BMI >95 percentile according to Italian Reference BMI charts. TSH, fT3 and fT4 were determined at baseline and after 6 months of lifestyle intervention. Fasting serum insulin, glucose, total cholesterol (TC), LDL, HDL and TG concentrations were also measured. Thyroid autoantibodies were measured in 72 OC; thyroid ultrasound (TU) was performed in 59.

**Results:** TF abnormalities were found in 109 OC (84 elevated fT3, 15 elevated TSH, 6 elevated fT4, 3 elevated fT3 and TSH, and 1 elevation of fT3, fT4 and TSH). TSH was not correlated with BMI-SDS. The prevalence TF abnormalities was similar between sexes and was not influenced by the pubertal stage. TU was abnormal in 3 out of 20 OC with abnormal TF and in 7 out of 39 OC with normal TF. Serum TC was similar between OC and C. LDL and TG were significantly higher in OC than in C, while HDL were significantly lower in the OC. BMI-SDS was negatively correlated with HDL. TF was not correlated with lipids. 43 OB with TF abnormalities were re-evaluated after 6 months. 33 of them had lost weight. TF normalized in 23 of the patients who lost weight and in 5 of the patients who did not.

**Conclusions:** Abnormalities of TF are a frequent finding in OC and do not correlate with BMI-SDS or with lipids. Moderate weight loss does not always restore these abnormalities, and normalization was also observed in patients who did not lose weight.

**P2-d1-450 Obesity and Fat 1**

**Usefulness of waist circumference measurement to identify children with high metabolic risk**

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It has been demonstrated that obesity is associated with insulin resistance and metabolic alterations that are risk factors for cardiovascular disease. Obesity in childhood has become a social problem and it has been recently published the first consensus on the definition of the metabolic syndrome in children. Aim of our study was to evaluate metabolic syndrome (MS) in a large group of obese children referred to our clinic using these IDF criteria. A cohort of 149 obese children, mean age (±SD) 10±3.0, prepubertal or in early puberty, underwent uXological evaluation, measurement of waist and hip circumference, blood pressure and basal metabolic blood evaluation. Oral glucose tolerance test (OGTT) was performed in 46 children. Two patients showed impaired fasting glucose, while 1 patient demonstrated diabetes mellitus and 2 impaired glucose tolerance (total glucose alterations: 3.4%), 3 children (2.0%) showed higher triglycerides levels, 29 (19.5%) had lower HDL levels, 21 (14.1%) had higher systolic and 27 (18.1%) had higher diastolic blood pressure. Mean waist circumference was 83.3±12.7 cm, while hip circumference was 91.5±13.4 cm. No sex differences were found for waist and hip measurements. Weight, height, BMI increased with age, but also waist and hip measures, systolic and diastolic blood pressure, ISI, HOMA and QUICKI indexes, triglycerides, fasting insulin levels. Waist and hip measures were strongly positively correlated with BMI, BMI percentile, systolic and diastolic blood pressure, HOMA index, insulin levels fasting and at 60 and 120 minutes after OGTT, triglycerides, alanine aminotransferase (ALT). Conversely, they were negatively correlated with ISI and QUICKI indexes. In conclusion, these preliminary results demonstrated that obese children of primary school already show metabolic alterations and suggest that as demonstrated in adults, also in children measurement of waist and hip circumference may be included in clinical practice and could be a simple method to identify children with higher metabolic risk.

**P2-d1-451 Obesity and Fat 1**

**Obelix: an experimental project to try to improve psychological outcome in obese adolescents**

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For several years we have been using an integrated intervention model for obese children and their parents. This model includes diet, endocrinological examinations and psychological support. Our previous studies seems to confirm the importance of behavioural and emotional aspects in the development and persistence of childhood obesity. This medical and psychological intervention model limited effect unless integrated with educational intervention to acquire a adequate lifestyle. Therefore we made a project for an educational group in Villaggio del Fanciullo’s structures for children between 10 and 15 years of age. Obelix Project. Children participated once a week having a meal together with a dietician, then a theatrical lesson (first period) and a multimedia work (second period), and then mild physical activity. The project was 6 months long. At the end they put on a show and a musical DVD was shown to their families and operators. Results. 9 children (5 M, CA 11.8±1.5yrs, BMIsds 2.8±0.5) took part. They were assessed using Achenbach’s and Rescorla’s Youth Self Report at the beginning and at the end. Obelix children, reported scores significantly higher than controls (normal weight matched for sex and age) in scales: anxious-depressed (p=0.048), somatic complaints (p=0.005), internalizing score (p=0.013), total score (p=0.012), affective problems (p=0.007), somatic problems (p=0.029). During the period children were not constant following the program, and the drop out was high. For this reason it was impossible to evaluate statistical differences in psychological outcome but, when recalled, most parents reported a scholastic and behavioural improvement. No positive changes were obtained in adiposity measurements. Conclusion. Adolescent obesity is difficult to treat, it is hard to maintain a motivation to change and drop out is high also in a non institutional structure. Psychological background of this kind of patients needs prepared operators. Our experience suggests that a heterogeneous group would be better than a group of only obese patients.

**P2-d1-452 Obesity and Fat 1**

**The prevalence of metabolic syndrome in obese Turkish prepubertal and pubertal children**

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**Aim:** Obesity associated with metabolic syndrome is characterized by glucose intolerance, insulin resistance, type II diabetes, dyslipidemia and other hormonal disorders in childhood. Unfortunately if the preventive measures are not taken in time they become obese in adulthood. The prevalence of metabolic syndrome in the pediatric age group is still not well known in our country. The
The relation between central adrenal insufficiency and sleep related breathing disorders in children with Prader-Willi syndrome

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The annual death rate of children with Prader-Willi syndrome (PWS) is high (3%). We reported an increased apnea-hypopnea-index in children with PWS, particularly during upper respiratory tract infection (URTI). It has been postulated that sleep apneas play a role in unsuspected deaths. Recently, however, we discovered that 60% of PWS patients suffer from central adrenal insufficiency (CAI) during stressful conditions. We, therefore, studied the relation between CAI and sleep apneas. Ten randomly selected PWS children were admitted for sleep monitoring during a metyrapone test (30 mg/kg at 2310h). ACTH and cortisol levels were measured at 0400h, 0600h and 0730h. CAI was diagnosed when ACTH levels were below 33 pmol/l at 0730h. We measured number and duration of central sleep apneas, desaturations, central-apnea-index and oxygenation-desaturation-index before and after metyrapone, until 0730h. Median (iqr) age was 7.3 (5.8-9.3) years. Six children had CAI. Median (iqr) central-apnea-index and oxygenation-desaturation-index were 4.2 (1.2-6.8) and 4.0 (3.4-5.1), respectively. There was no significant difference in sleep related breathing between children with CAI and those without. Central-apnea-index was significantly higher after 2330h (during the metyrapone test) than before (p=0.02). This was most likely due to difference in sleep stages, because no correlation was found with cortisol and ACTH levels. Our data do not show more central sleep apneas in PWS children with CAI who are in a healthy condition. However, we previously reported an increase in median (iqr) apnea-hypopnea-index during URTI from 5.7 (3.1-9.5) to 36.5 (18.1-39.5). Our data suggest that a combination of CAI and severely increased sleep apneas during acute illness may lead to a fatal cascade.

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Results: Metabolic syndrome was found in 18.8 % cases. Metabolic syndrome was found in a significantly higher rate in the pubertal group than in the prepubertal group. The data related with glucose homeostasis; fasting hyperinsulinemia, impaired glucose tolerance were 33.3% and 5.5% in the prepubertal group, respectively. The same data fasting hyperinsulinemia, and impaired glucose tolerance were 64.7% and 23.5% in the pubertal group, respectively. Hypertension was observed in four pubertal cases (11.7%). Dyslipidemia in prepubertal and pubertal groups were identified in 41.6% and 41.1%, respectively, with no significant differences.

Conclusion: Metabolic syndrome prevalence especially abnormal glucose homeostasis among the obese pediatric age group were quite high. Early diagnosis, regularly follow-up and if needed, treatment will be prevent beta-cell destruction and development of type 2 diabetes mellitus.

P2-d1-453 Obesity and Fat 1

Long-term follow-up of changes in anthropology and glucose metabolism in obese children

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Multiple treatment options for obese children exist; however, improvements of anthropometric and metabolic parameters are rarely evaluated over a longer duration of time. Our objective was to investigate long-term changes in anthropometry and glucose metabolism. All 89 obese children (BMI-SDS 2.8 ± 0.5) who underwent an oral glucose tolerance test at our clinic between 2001 and 2003 were invited 3-6 years later for re-evaluation. At their initial presentation to our clinic, their families had been advised to participate in local treatment options. After a mean follow-up of 4.8 years, all of the 23 participating children were still obese (BMI-SDS 3.0 ± 0.6). Treatment form or intensity did not differ between those children, who improved their BMI-SDS (n = 8; 35%) and those who did not (n = 15; 65%). The only difference between these groups was age at onset of treatment. On average, the younger children (change in BMI-SDS: -0.3 ± 0.3 versus +0.2 ± 0.7, p < 0.05). Contrary to this, the prepubertal children showed a deterioration of glucose metabolism with a marked increase in insulin increment (+253.7 ± 333.7) and a decrease in ISI (-1.9 ± 0.8) whereas insulin increment in the older children improved (-27.7 ± 264.8) and ISI remained unaltered (0.0 ± 1.8; for both comparisons p < 0.01) Because of the small number of participants, a generalisation of our results has to be treated cautiously. However, prepubertal children seem to have an increased risk of deterioration in glucose-metabolism despite improvement in BMI-SDS. This might be due to progression of puberty in this age-group. It is also remarkable that over an average observational period of 4.8 years, form and intensity of treatment did not show any influence on BMI-SDS changes.

P2-d1-455 Obesity and Fat 1

Body composition and cardiovascular risk factors in survivors of bone marrow transplantation (BMT) in childhood

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Background: There is emerging evidence that BMT survivors not only suffer long term endocrine sequelae, but also have increased risk of cardiovascular disease T2DM. We examined body composition and cardiovascular and metabolic risk factors in adolescent and young adult survivors.

Method: We enrolled 31 BMT survivors (14F,17) were pubertal, and 18 were post pubertal. We measured body composition by DEXA scan and BMI, and fasted lipids and HSCRP. They were compared with 13 (6F) age matched non BMT survivors. All subjects had GH status assessed and 28 BMT survivors and 4 controls were growth hormone deficient. 19 of the survivors and none of the controls were on GH treatment at the time of testing.

Results:

<table>
<thead>
<tr>
<th>% body fat</th>
<th>BMISDS</th>
<th>T.chol</th>
<th>LDL</th>
<th>HDL</th>
<th>ratio</th>
<th>Triglycerides</th>
<th>HSCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>22.5 (12.7)</td>
<td>-0.09 (1.84)</td>
<td>3.02 (0.74)</td>
<td>1.96 (0.50)</td>
<td>1.48 (0.61)</td>
<td>2.8 (0.52)</td>
<td>0.82 (0.39)</td>
</tr>
<tr>
<td>Survivors</td>
<td>32.2 (11.7)*</td>
<td>0.29 (1.50)</td>
<td>4.81 (0.60)**</td>
<td>2.57 (0.43)**</td>
<td>1.58 (0.40)**</td>
<td>3.3 (0.81)</td>
<td>1.62 (1.15)</td>
</tr>
</tbody>
</table>

All results Mean (SD) *p<0.05, **p<0.005, ***p<0.0005
BMI is a poor indicator of adiposity in this group due to their short stature and reduced lean mass. The BMT survivors have higher % body fat than controls despite a normal BMIDS. Female survivors have higher body fat than male survivors (39.0% vs 26.8%), and HSCR is higher, although lipids are similar. Total cholesterol was high or borderline high in 14 survivors. 6 have borderline high LDL and 18 have a total/HDL ratio above the recommended level of 3. Lipid abnormalities did not show any relationship to growth hormone status. 10 survivors also had OGTts, of which 5 show impaired glucose tolerance, and 4 show diabetes mellitus.

Conclusion: BMT survivors have a high rate of abnormal body composition and lipid profiles. These are more pronounced in females. Future studies should investigate the benefits of early targeted interventions to improve body composition, lipid profiles and metabolic health.

P2-d2-456 Adrenal 2

Frequency of non-classical congenital adrenal hyperplasia in 100 girls with hirsutism and premature pubarche
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Objective: Non Classical CAH (NCAH) is the most common autosomal recessive disorder in human. The prevalence is 1-6% among hyperandrogenic women. The purpose of this study is to determine the frequency of NCAH in hyperandrogenic girls in Iran.

Method: 100 girls with hyperandrogenic symptoms (12 premature Pubarche PP, 88 hirsutism ± oligomenorrhea) were enrolled in this study. Mean ± SD for premature Pubarche and hirsutism grading ≥ 8 was considered as hirsutism. Fasting DHEAS, Androstenedione, 17OH-Pregesterone (17OHP), Pregesterone Testosterone, and Cortisol were measured at 8:00 AM in the follicular phase (days3-10) and one hour after 250 μg IV injection of short acting ACTH. All measurements were done by RIA method. NCAH and heterozygote patients were defined by 17OHP after ACTH ≥1500 ng/dl and ≥ 430 ng/dl respectively. T test and ANOVA were used for quantitative variables and Chi2 and Fisher tests were used for qualitative variables.

Results: Three NCAH (3.4%) and 22 heterozygote patients (22.7%) were in hirsute group. 5 girls with PP (41.7%) had criteria of heterozygote group. All NCAH patients had basal 17OHP>200 ng/dl. The PPV for 17OHP> 200 ng/dl and VPV for 17OHP> 200 ng/dl was 21.4% and 100% respectively. The 17OHP after ACTH in NCAH were 55.1 to 126 higher than upper normal range. The hirsutism score was significantly higher in normal than in heterozygote patients (P=0.02). The basal and post ACTH, 17OHP were higher in heterozygote than normal group (P=0.03 and P<0.001). There was no significant difference in other variables between these two groups.

Conclusion: The overall frequency of NCAH in Iranian hyperandrogenic girls is 3%. To respect this frequency the ACTH test do not recommend routinely for patients with hyperandrogenism.

P2-d2-457 Adrenal 2

Prenatal treatment of congenital adrenal hyperplasia (CAH): Neuropsychological studies in children and young adults exposed to dexamethasone before birth
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Background: Prenatal treatment of CAH is undoubtedly beneficial for affected girls. Several questions are still unresolved regarding long-term consequences of exposure to dexamethasone (DEX) in all treated fetuses - both affected and unaffected.

The Aim of the Study was to assess lateralization, cognitive development and memory functioning in CAH patients and their healthy siblings treated prenatally with DEX.

Patients: 35 children and young adults (19 F / 16 M) from 17 families at risk for CAH, aged from 6.7 to 23 yrs (median 13 yrs); 23 were CAH-affected, 12 unaffected; 20 were treated prenatally with DEX.

Methods: standardized neuropsychological tests: WAIS-R or WISC-R, Rey Auditory Verbal Learning Test, DCS - Visual Learning and Memory test for Neuropsychological Assessment, hand-preference tests. Taking into account: presence of the disease, administration of DEX, sex of patients - six groups were distinguished: CAH girls untreated, CAH girls treated, healthy girls treated, CAH boys untreated, CAH boys treated, healthy boys treated. Long-term DEX treated were CAH girls, whereas boys and healthy girls were mostly short-term treated.

Results: in patients with CAH (regardless of DEX treatment) left-handedness was significantly more frequent (p=0.005). Performance on tasks involving working memory were scored lower in long-term treated children in comparison with short-term treated (difference statistically significant or on the level of trend, ranging from p=0.03 to p=0.01 for particular tests). Visuospatial analysis tests were significantly worse in treated healthy girls than in children from other groups (p=0.02). However, all these results were within the normal range of age-related values.

Conclusions: Left-handedness was statistically more frequent in studied CAH patients. Long-term prenatal DEX treatment may influence the postnatal impairment of working memory. Even short-term prenatal administration of DEX could result in lowering of visuospatial abilities in healthy girls treated.

P2-d2-458 Adrenal 2

An adrenal rest tumour in the perirenal region of a patient with congenital adrenal hyperplasia (CAH) due to 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency
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Background: In contrast to the high incidence of testicular adrenal rest tumours (TART) in adult male CAH patients (up to 94%), ovarian adrenal rest tumours in female CAH patients are very rare and other locations of adrenal rest tumours in adult CAH patients have never been reported. Here, we report on an adult patient with CAH due to 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency with bilateral TART and additionally a large perirenal adrenal rest tumour.

Case Report: The patient was known with CAH due to 3β-HSD deficiency and treated with hydrocortisone and fludrocortisone since the neonatal period. Since the pubertal period there was lack of compliance with consequently high plasma ACTH concentrations. At the age of 16 years bilateral TART were detected by scrotal ultrasound. Intensifying glucocorticoid medication did not result in decrease of plasma ACTH concentrations and shrinkage of the size of the tumours. At the age of 23 years abdominal ultrasound was performed because of complaints of nausea and vomiting, showing a round inhomogeneous structure with a diameter of 4 cm retroperitoneal near the left renal hilus. A computer tomography (CT) scan showed a multinodular lesion of 3.4 x 4.5 cm in the retroperitoneal region beside the left kidney without pathological lymph nodes. Histological investigation after removal of the tumour showed sheets of large polygonal cells with abundant eosinophilic cytoplasm, separated by dense fibrous tissue strands. The histological and immunochemical profile resulted in a diagnosis of an adrenal rest tumour.

Conclusion: In adult CAH patients ectopic adrenal rest tumours can be present outside the testicular region. Further investigations will be necessary to determine whether regularly screening for these tumours is useful.
A homozygous R496C mutation in the CYP17A1 gene causes a severe disorder of sexual differentiation

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Introduction: 17 hydroxylase/17,20-lyase (CYP17A1) deficiency is a disorder of steroidogenesis, characterized by relative cortisol deficiency and impaired androgen synthesis causing a female external phenotype in spite of 46XY karyotype. We describe severe 17,20-lyase deficiency caused by a homozygous gene mutation.

Methods/Patients: 2 cousins with 46XY karyotype from consanguineous families, presented neonatally with a female phenotype following extremely low gestational estriol levels. Clinical evaluations were followed by DNA extraction for micro-satellite linkage analysis and sequencing of the CYP17A1 gene.

Results: Blood pressure and electrolytes were consistently normal. Cortisol levels stayed in the low-normal range without replacement therapy. ACTH stimulation failed to raise the low 17OHpregnenolone, 17OHprogesterone (17OHP), DHEAS or testosterone. The initially high aldosterone levels decreased drastically at 2-4y of age. Both patients reared as females underwent gonadectomy at 1.5y and 3y of age. The gonad(tes)tes) showed occasional PLAP and C-kit positive germ cells in tubular lumena and along basement membranes consistent with maturation delay. Using microsatellite markers (D10S192,597,1709) flanking the gene we found both patients to be homozygous and their parents heterozygous at the CYP17A1 gene locus. Sequencing revealed a homozygous (C-T) mutation predicting a substitution of Arginine to Cysteine at the 496 amino acid (R496C) of CYP17A1 protein in both patients.

Conclusions: The R496C homozygous mutation in CYP17A1 gene causes severe androgen deficiency and male to female phenotypic change. The presence of cortisol in spite of undetectable 17OHP may suggest cortisol production by alternative bypassing pathways. The initial high aldosterone decreasing later to undetectable levels may support the hypothesis that a gradual increase in deoxycorticosterone eventually suppresses aldosterone and ACTH secretions. Finally, the significance of C-kit positive germ cells in the 3y old patient gonads is unknown. Early gonadectomy may be warranted.

Pharmacokinetics of clinical hydrocortisone and cortisone administration

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During glucocorticoid (GC) replacement, the bioavailability of GC is influenced by absorption rate and clearance. To evaluate the optimal dose, we studied 11 patients with hypopituitarism after removal of a pituitary tumor (Group 1) and 12 patients with primary adrenal disease (Group 2). Ponderosity was assessed by BMI and umbilical CT for sc and visceral fat. After withdrawal of GC replacement for 24 hr, basal 8 am serum cortisol (F) levels were <22 - 68 nmol/L (n 190-690 nmol/L). Following a single dose of 12 mg/m2 HC acetate, 1 patient showed a wide variation of peak F levels (Cmax) from 462-2459 nmol/L, with peak F after 2-4 hours (TCmax). After 15 mg/m2 C, it was 233-1570 nmol/L. No correlations were found between Cmax and BMI, total body fat, truncal fat, extremities fat, sc or visceral fat following either HC or C.

1. Individual GC pharmacokinetics vary widely. 2. It is suggested to use F pharmacokinetics as a clinical test, and to adjust the replacement dose accordingly.

The novel Star mutation N148K causes 46,XY-DSD with complete sex reversal and congenital lipoid adrenal hyperplasia

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Congenital lipoid adrenal hyperplasia is a rare autosomal recessive disorder of steroidogenesis characterized by diminished or absent synthesis of all adrenal and gonadal steroids. Mutations in the steroidogenic acute regulatory protein (StAR) have been identified. Herein, we describe a novel STAR mutation detected in a girl manifesting with failure to thrive and apparent salt-loss at age 3 months. Clinical examination revealed normal female external genitalia and hyperpigmentation of the skin. Hormonal work up showed elevated ACTH and PRA and low aldosterone levels. Cortisol, dehydroepiandrosterone, 17-hydroxyprogesterone and testosterone were in the low normal range. MRI demonstrated enlarged adrenal glands and absence of uterus. Small gonads were detected in the groins. Karyotyping revealed a 46, XY condition. Gonadectomy was performed at age 17 months. Molecular analysis of the STAR gene from genomic DNA and reverse transcribed gonadal RNA revealed a homozygous missense mutation (c.444C>A in exon 4, N148K). Both consanguineous parents were heterozygous for this mutation. Transient in vitro expression of the mutant protein together with P450scc, adrenodoxin and adrenodoxin reductase yielded a severely diminished conversion of cholesterol. As deduced from our 3D protein model, the residue N148 is lining the ligand tunnel of StAR and is likely to be involved in ligand interaction. The exchange of the polar asparagine with basic lysine disturbs the interactions with cholesterol and therefore inactivates StAR. The excised gonads showed immature Sertoli cells and scattered germ cells and spermatogonia within the seminiferous tubules. As expected at this age, Leydig cells were not visible and staining with an inhibin and STAR antibody was negative. The functional STAR analysis fully explains the patient’s clinical phenotype. Our study demonstrates that combining in vitro expression studies with protein structure analysis is a powerful tool for providing new insights into STAR. This also provides important additional information for proper patient management.

Analysis of MC2R and MRAP genes in six infants with ACTH resistance

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Inherited adrenocorticotropic (ACTH) resistance diseases are rare and include triple A syndrome and familial glucocorticoid deficiency (FGD). In FGD patients, mutations in melanocortin 2 receptor (MC2R) and in MC2R accessory protein (MRAP) have been described, although 55 % of patients do not have a mutation in these genes.

Objective: To analyse MC2R and MRAP genes in six infants with isolated ACTH resistance.

Patients and Methods: Six patients (3 boys) from 5 families, diagnosed of congenital isolated ACTH resistance based on: 1) low cortisol (< 5 mg/dl) with high ACTH (> 500 pg/ml); 2) no evidence of mineralocorticoid deficiency; 3) diagnosis during the first 2 years of life; 4) no associated autoimmune diseases; 5) adrenal ultrasound that ruled out haemorrhagic or infectious disorders; 6) 17-OH-progesterone < 200 ng/dl; and 7) absence of alacrimia or achalasia. DNA was extracted from peripheral blood leukocytes and automated sequencing of MRAP and MC2R genes was performed.

Results: Clinical characteristics. Age at diagnosis: 9.3 ± 6.2 months (1.5-15.1). Initial clinical manifestations: hypoglycaemia (n=6), hyperpigmentation.
(n=6), asthenia (n=3), hypotension (n=2), hyponatraemia with normal potassium (n=1) and hypoglycaemic seizure (n=1). Hormonal and biochemical parameters at diagnosis were: glucose 34.7±7.4 mg/dl (25-43); sodium 131.0 ± 3.3 mEq/L (127-135); potassium 4.4 ±0.6 mEq/L (3.9-5.1); Cortisol 1.2±0.8 mg/dl (0.5-2.6); and ACTH 1124.3± 128 pg/ml (863-1250). Genetic study Analysis of the MC2R gene: in patient 6, mutation 156insA (K298fs) was found in homozygosis. The consanguineous parents, 1 sister and 2 brothers of this patient were studied and the same mutation was found in heterozygosis in all. No mutations were found in the other patients. Analysis of the MRAP gene: no mutations were found in the five patients without mutations in the MC2R gene.

Conclusions: The observed frequency of mutations in the MC2R gene was 1/5 families and no mutations in the MRAP gene were found.

**P2-d2-463 Adrenal 2**

Hydrocortisone content in capsules for the treatment of congenital adrenal hyperplasia

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Goal of the medical treatment in congenital adrenal hyperplasia (CAH) therapy is to replace deficient steroids while minimizing adrenal sex hormone and glucocorticoid excess, preventing virilization and optimizing growth. During infancy hydrocortisone (HC) is considered the drug of first choice for therapy and should be used in growing children with a typical dosing of about 10–15 mg/m²/day divided in three times daily. For that purpose in Germany capsules are manufactured individually in pharmacies with a prescribed, but uncertain content per capsule of about 0.5 to 9 mg depending on the child’s age, because the lowest available content of an industrial manufactured capsule is 10 mg. Members of the EndoWest-quality circle collected HC-capsules from their CAH-patients to assay the content of HC. Quantitative determination of HC content of these capsules was performed by LC/MS (liquid chromatography/mass spectrometry) after dissolving the capsules’ content in a methanol/water mixture. The content of 48 capsules could be analyzed, with a prescribed content of HC ranging from 1 mg to 9 mg per individual capsule. The percental difference between the real and the prescribed content of HC ranged from -52% to +20%. Five samples contained equal or more than 10% and one more than 20%, and 26 samples contained equal or less than 10% and 10 equal or less 20% HC under the prescribed concentration. As a mean the difference between the real and the prescribed HC-content was 13% with a standard deviation of 10%. We found relevant differences between the real and the prescribed content of HC in pharmacy manufactured capsules for individualized therapy of CAH. We demand a better quality control in the pharmacy-based production of HC-capsules, far better would be an industrial production of HC-preparations in lower dosages.

**P2-d2-464 Adrenal 2**

Evaluation of adrenal axis in 3-7 years asthmatic children treated with moderate doses of fluticasone propionate: Reliability of dehydroepiandrosterone sulphate as a screening test

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Background: Inhaled corticosteroids (ICS) are the first line therapy in the treatment of persistent asthma. At medium to high doses and prolonged usage ICS can suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use of fluticasone propionate (FP) has been reported to cause dose related HPA suppression greater than that of other commercially available ICS. There are various tests used to evaluate HPA axis. Use of dehydroepiandrosterone sulphate for assessment of adrenal suppression has been recommended. Dehydroepiandrosterone sulphate (DHEA-S) is a corticotropin-dependent adrenal androgen precursor that may be suppressible in patients treated with ICS.

**Objectives:** To evaluate the adrenal axis in asthmatic children treated with moderate doses of FP and to evaluate the DHEA-S as a possible marker for HPA axis in a small age group, preadrenarchial children.

**Methods:** 28 Children with persistent asthma with a mean age of 4.4 (2.5-7.1)(median 4.2) years on long term treatment (4.5-9 months)(mean 6.16, median 6) with moderate doses (158-347 µg/m²/day)(mean 250, median 253) of inhaled FP were evaluated with low dose ACTH stimulation test (LDAT) to assess HPA axis and DHEA-S levels were compared with the results.

**Results:** One out of 28 patients (3.57%) demonstrated an normal cortisol response to LDAT. There was no correlation between DHEA-S and peak cortisol, morning cortisol and fasting blood glucose levels. However there was negative correlation between mean FP dosages and DHEA-S level.

**Conclusions:** It seems to be safe use of moderate FP dosages in asthmatic children in terms of adrenal suppression. DHEA-S levels did not correlate with the fasting blood glucose, morning cortisol levels and peak cortisol levels. We found that, when ICS dosages increase, DHEA-S levels decrease. Chronic moderate dose ICS can suppress adrenal androgen levels without suppression of cortisol production. Thus DHEA-S levels can be used as a practical method to follow adrenal functions and may be an earlier indicator of adrenal suppression in children.

**Keywords:** asthmatic children, dehydroepiandrosterone sulfate, adrenal suppression, fluticasone propionate

**P2-d2-465 Adrenal 2**

Serum levels of Dehydroepiandrosterone Sulfate (DHEAS) in children with classic congenital adrenal hyperplasia due to 21-Hydroxylase Deficiency (CAH)

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**Objective:** There have been only a few studies on adenarche in CAH patients showing that DHEAS levels did not rise in well controlled patients at the physiological age of adenarche. Thus, we have analysed longitudinally the serum DHEAS levels in CAH children in relation to chronological age, Tanner stages, and various parameters such as medication or quality of metabolic control.

**Methods:** We studied 98 CAH patients (51 f; 47 m), aged between 1.0 and 18.0 years (median 8.7). All patients had genetically proven classic CAH (salt wasting, simple virilizing) and received standard steroid substitution therapy. DHEAS levels were measured by in-house ELISA and compared with an age and sex-matched group of healthy children (n=508). For the analysis of the Tanner stages, we used the data published by J. Buckler. For statistical analyses we used standard parametric tests.

**Results:** Serum DHEAS levels were not different between CAH children and normal children from 1 yr until the age of 5-6 yrs. However, starting from the age of 7-8 yrs, there was a continuous but blunted increase in DHEAS levels in CAH boys and girls in comparison to normal children. In other words, DHEAS levels in CAH children were significantly lower than in normal children (Fig. 1). There was no correlation of DHEAS levels with the genotype, glucocorticoid doses, auxological data or quality of metabolic control. There was no difference between the clinical forms. Despite lower DHEAS levels, pubarche (PH2) and Tanner stages PH3 and PH4 occurred significantly earlier in CAH boys and girls (PH2: boys: 7.2 ±2.9; girls: 9.6 ±2.1; p<0.0001) than in the reference group.
Concomitant ectopic and intra-adrenal adenomas of the adrenal cortex

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Adenomas of the adrenal gland are a rare cause of virilization in childhood. We illustrate a 2 6/12 years old girl with precocious pseudopuberty. The girl presented with pubarche, distinct clitoral hypertrophy, tall stature (102 cm, SDS 2.94) and increased height velocity (10.5 cm/y, SDS 1.9). Imaging of the adrenal glands was performed by ultrasound examination, MRI and Norcholestrol scintigraphy. DNA was extracted from the tumor in order to examine the expression of the melanocortin-2 receptor (MC2R) and the LH-receptor. Plasma testosterone (204 ng/dl) and DHEA (71 ng/dl) were elevated also were precursors of embryonic steroids detected, e.g. epiandrosterone and 16alpha-DHEA. Androgens remained unchanged after ACTH, [h-HCG] and dexamethasone administrations. The bone age (Greulich and Pyle) was accelerated (4 2/12 years). Ultrasound examination and MRI indicated an extra-adrenal mass adjacent and caudal to the left adrenal gland, which was removed by endoscopic surgery. However, plasma androgens remained high and Norcholestrol scintigraphy revealed a tracer enhancement in the right adrenal gland, which was consecutively removed. Histology revealed in the right adrenal gland a circumscribed adenoma with mainly oxophilic components and in the left sided tumor an oxophilic epithelial mass with adrenal cortical cells. MC2R expression was augmented threefold compared to control and only low expression of the LH-receptor was detected. Virilization regressed after extirpation of the adenomas and height velocity decreased to 6.79 cm/y (SDS = 0.90). Our findings underline that androgen producing adenomas may be located within and/or outside of the adrenal cortex and may provoke severe virilization in prepubertal girls. Specific scintigraphy, when available, assists in allocating the source of androgen hyperssecretion. Furthermore, we demonstrated that the adenoma derived from the adrenal cortex because the expression of MC2R was elevated. Long-term follow up is warranted to assure complete removal of the adenomas.

Salt wasting congenital adrenal hyperplasia: Ethnic genotypical peculiarities

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Here we report for the first time the results of the molecular study of 17 unrelated patients with salt wasting (SW) congenital adrenal hyperplasia (CAH) belonging to Sicilian ethnic group, as corroborated by patients’ pedigree taken to include two generations in the paternal and maternal lineage. Aim of this report was to confirm that genetic basis of CAH may be characterized by population differences. In our series the overall predominant mutation was IVS2A/C>G, that was detected in 50% of alleles and in 58.8% of patients. The allelic and homozygous frequencies of IVS2A/C>G, Del8bpE3 and R356W mutations were significantly higher in our series than in other populations. Our study population included 2 cases with two different mutations that have been recently reported for the first time, 3 cases with two double mutations on the same allele and 1 case with homozygous de novo mutation. We concluded that: a) in Sicilian ethnic group the most frequent genotype in SW CAH is IVS2A/C>G homozygocity b) surprisingly Del8bpE3 and R256W homozygocity are also well represented.

Conclusion: Adrenarche in CAH children occurs at the same time than in healthy children, but in comparison with healthy children, the increase of the DHEAS levels was flattened during the course of puberty.

Adrenal function during childhood and the onset of puberty in daughters of women with polycystic ovary syndrome (PCOS)

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Context: PCOS is a common familial endocrine-metabolic disorder. In some patients with PCOS the syndrome may develop as a consequence of an exaggerated adrenarche during pubertal development, which may be related to the presence of hyperinsulinemia.

Objective: To assess adrenal function during childhood, and pubertal development in daughters of women with PCOS (PCOS-d). Design: Sixty eight PCOS-d [57 prepubertal (4-8 yr old) and 11 peri-pubertal (9-13 yr old) and 35 daughters of control women (C-d) [27 prepubertal and 8 peri-pubertal ] were studied. In both groups, an acute ACTH-(1-24) stimulation test (0.25 mg cosyntropin®, Organon) and an OGTT were performed. Bone age and the serum concentrations of cortisol, dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEAS), androstenedione, 17-hydroxyprogesterone, glucose, and insulin were assessed.

Results: PCOS-d and C-d were similar in age and BMI SDS. In PCOS-d, basal DHEAS concentrations were higher compared to C-d (43.9 ± 37.5 vs. 33.6 ± 20.2 ug/dl, mean ± SD, p=0.03). However, post-stimulated DHEAS concentrations were similar between both groups. In C-d, but not PCOS-d, a
increase in the DHEAS response to stimulation between the prepubertal and peripubertal period was observed (p=0.016). There were no differences in the other hormone concentrations pre and post-ACTH stimulation between PCOS-d and C-d. Post-stimulated insulin was higher in PCOS-d compared to C-d during the prepuberty (p=0.03) and peripuberty (p=0.03). An advancement of six months was observed between bone and chronological age in peripubertal PCOS-d.

Conclusions: In PCOS-d, DHEAS concentrations are higher during child-
hood and remain elevated during the onset of puberty, although without a difference in the response to ACTH administration, suggesting differences in DHEA sulfation. A modest and temporary advancement in bone age was observed, possibly secondary to the adrenal hyperandrogenism. PCOS-d also demonstrate higher insulin levels, which may play a role in both the adrenal dysfunction and the advanced bone age. Supported by FONDECYT Grant 1071007

**P2-d2-469 Adrenal 2**

**A clinical test in women for DHEA sulfotransferase (ST) and 11β-HSD type 1 activities**

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**Objective:**

To develop a clinical test to assess the activity of DHEA ST and 11β-HSD-1.

**Methods:**

Young healthy women, n=24, age range 18-32 y, participated in the study during their follicular phase. To suppress endogenous adrenal activity, they received 2 mg DEX 24 h prior to the test. A blood sample for DHEAS and cortisol (F) was taken at 0900 as a baseline. The enzymes' substrates DHEA and cortisol acetate were orally administered at 25 and 50 mg/sm, respectively. Blood samples for the DHEA-ST product DHEAS were taken 1 and 2 h later, and samples for 11βHSD-1 product F were taken 1, 2 and 4 h later.

**Results:**

Following a 24 h HPA axis suppression, serum F was 152 ± 169 nmol/l (mean ± SD). By 1, 2 and 4 h, F levels increased to 853 ± 406, 1087 ± 460 and 1056 ± 487 nmol/l, an increase of 702 ± 436, 935 ± 482 and 904 ± 503 nmol/l, resp. The basal DHEAS levels after 24 h HPA axis suppression were 3 ± 2 µmol/l. It increased to 6.6 ± 2.8 and 10.7 ± 3.1 µmol/l by 1 and 2 h, resp., an increase of 3.6 ± 2.2 and 7.7 ± 3.2 µmol/l, resp. DEX-suppressed F correlated positively with DEX-suppressed DHEAS (r=0.422, p<0.05). F generation by 11βHSD-1 correlated negatively with BMI (r=0.479, p<0.02) and positively with age (r=0.461, p<0.02). DHEAS generation by ST did not correlate with age or BMI. 11βHSD-1 and ST activities correlate positively with each other (r=0.726, p<0.005).

**Conclusions:**

We offer a simple clinical test to evaluate prerreceptor intracrine deactivation of DHEA by ST and cortisone activation by 11β-HSD-1. 2. Whereas 11β-HSD-1 expression is increased in obesity, it correlates negatively with BMI in healthy women. 3. 11β-HSD-1 activity increase with age among young women. 4. 11β-HSD-1 and ST correlate positively, whereby we do not know if activation of glucocorticoids stimulates the deactivation of the androgen, or deactivation of DHEA stimulated paracrine F generation.

**P2-d2-470 Adrenal 2**

**Adrenal suppression following intralesional steroids for periocular haemangiomata**

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Intralesional triamcinolone (a potent corticosteroid) is currently recommended as the treatment of choice for infantile sight-threatening periocular haemangiomata. Several case reports have suggested endogenous adrenal suppression following such treatment. Currently we treat all such babies with low dose maintenance hydrocortisone cover until adrenal recovery. This study investigates the auxological and endocrine changes in 15 babies treated with intralosal triamcinolone over a 10 year period in one centre. All infants receiving intra/perilesional triamcinolone for periocular haemangiomata from 1996-2007 had measurements of early morning serum cortisol and ACTH prior to and following injection along with auxological measures (which were converted to standard deviation scores (SDS)) Mean post gestational age of babies at injection was 22.5 weeks (range 10-56 weeks). There was a fall in serum cortisol from a mean (SD) of 344 (165.6) to 65.7 (128.5) nmol/l (p=0.0007) and mean (SD) ACTH, which fell from 38 (35.2) to 11.3 (5.2) ng/l (p=0.034) between pre injection and 4 weeks post-treatment. Prolonged suppression of cortisol and ACTH was noted in 13 out of 15 cases with the mean time to recovery of adrenal function being 25.4 weeks (range 4-60 weeks). Failure to thrive was observed until adrenal recovery in all 15 cases (figure).

**Introduction:**

Prereceptor intracellular modification converts active DHEA into its inactive sulfate ester by ST, and inactive cortisone into active cortisol by 11β-HSD type 1.

**Objective:**

To develop a clinical test to evaluate the activity of DHEA ST and 11β-HSD-1.

**Methods:**

Young healthy women, n=24, age range 18-32 y, participated in the study during their follicular phase. To suppress endogenous adrenal activity, they received 2 mg DEX 24 h prior to the test. A blood sample for DHEAS and cortisol (F) was taken at 0900 as a baseline. The enzymes’ substrates DHEA and cortisol acetate were orally administered at 25 and 50 mg/sm, respectively. Blood samples for the DHEA-ST product DHEAS were taken 1 and 2 h later, and samples for 11βHSD-1 product F were taken 1, 2 and 4 h later.

**Results:**

Following a 24 h HPA axis suppression, serum F was 152 ± 169 nmol/l (mean ± SD). By 1, 2 and 4 h, F levels increased to 853 ± 406, 1087 ± 460 and 1056 ± 487 nmol/l, an increase of 702 ± 436, 935 ± 482 and 904 ± 503 nmol/l, resp. The basal DHEAS levels after 24 h HPA axis suppression were 3 ± 2 µmol/l. It increased to 6.6 ± 2.8 and 10.7 ± 3.1 µmol/l by 1 and 2 h, resp., an increase of 3.6 ± 2.2 and 7.7 ± 3.2 µmol/l, resp. DEX-suppressed F correlated positively with DEX-suppressed DHEAS (r=0.422, p<0.05). F generation by 11βHSD-1 correlated negatively with BMI (r=0.479, p<0.02) and positively with age (r=0.461, p<0.02). DHEAS generation by ST did not correlate with age or BMI. 11βHSD-1 and ST activities correlate positively with each other (r=0.726, p<0.005).

**Conclusions:**

We offer a simple clinical test to evaluate prerreceptor intracrine deactivation of DHEA by ST and cortisone activation by 11β-HSD-1. 2. Whereas 11β-HSD-1 expression is increased in obesity, it correlates negatively with BMI in healthy women. 3. 11β-HSD-1 activity increase with age among young women. 4. 11β-HSD-1 and ST correlate positively, whereby we do not know if activation of glucocorticoids stimulates the deactivation of the androgen, or deactivation of DHEA stimulated paracrine F generation.

**Impact of total cumulative glucocorticoid dose on bone mineral density in patients with 21-hydroxylase deficiency**

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**Background and Objectives:**

It remains controversial whether long-term glucocorticoids are charged of bone demineralization in patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. The aim of this study was to know if cumulative glucocorticoid dose from the diagnosis
in childhood to adulthood in patients with CAH had a negative impact on bone mineral density (BMD).

**Population and Methods:** This was a retrospective study. Thirty-eight adult patients with classical and non-classical CAH were included. BMD was measured in the lumbar spine and femoral neck. Total cumulative (TCG) and total average (TAG) glucocorticoid doses were calculated from pediatric and adult files. Results: We showed a difference between final and target heights (-0.82±0.92 SD for women and -1.31±0.84 SD for men; p<0.001). Seventeen patients (44.7%) had bone demineralization (35.7% of women and 70% of men). The 28 women had a higher BMD than the 10 men for lumbar (-0.26±0.80 SD vs. -0.12±0.10 SD; p<0.02) and femoral T-scores (0.21±1.30 SD vs. -0.02±1.10 SD; p=0.007). In the salt-wasting group, women were almost significantly endowed with a better BMD than men (p=0.053). There was a protective effect of BMI on BMD (p=0.006). We found negative effects of TCG, TAG on lumbar (p<0.001 and p=0.002) and femoral T-scores (p<0.006 and p=0.001).

**Precise Conclusions:** The total cumulative glucocorticoid (TCG) dose is responsible for a bone demineralization in patients with 21-hydroxylase deficiency. We should adapt glucocorticoid treatment and discuss preventive measures in order to limit this effect.

**P2-d2-473 Adrenal 2**

**The effect of glucocorticoid replacement therapy and androgen levels on bone mineral density in children and adolescents with congenital adrenal hyperplasia**

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The patients with congenital adrenal hyperplasia (CAH) are treated with physiological doses of glucocorticoids. Long term treatment with glucocorticoids and androgen excess have opposite effects on bone mineralization. Aim of this study is to assess bone mineral density (BMD) in patients with CAH and to evaluate the effects of androgen excess and/or glucocorticoid replacement dose on BMD. Forty-nine patients with CAH (43 patients with 21 hydroxylase deficiency (26, simple virilizing-SV; 11, salt wasting-SW; 6, non-classic), 6 patients with 11 hydroxylase deficiency) were included in the study. Age range was 3.2–21.5 years. Lumbar spine BMDs, obtained using DEXA, were compared to 53 age, sex and pubertal stage matched healthy children. Mean values of serum 17-hydroxyprogesterone and 11 deoxycortisol levels were analyzed during follow-up period. Daily glucocorticoid replacement dose was evaluated against body surface area.

Patients with CAH had similar BMD z-score with controls but higher mean body mass index (BMI) z-score than control group. When we evaluated according to pubertal stage both BMD and BMI z-scores of prepubertal patients were significantly higher than controls. Patient group was classified according to BMI z-score into below and above 1.5 SD. BMD z-score was significantly lower in patients with a BMI z-score below 1.5. When BMD z-scores were evaluated according to type of enzyme deficiency, patients with 11 hydroxylase deficiency and SW-21 hydroxylase deficiency had lower BMD z-scores compared to SV-21 hydroxylase deficiency. (-0.78±0.8; 0.84±1.0; 0.22±1.62 respectively). There was a positive correlation between serum 17-hydroxyprogesterone level and BMD z-score in patients with 21 hydroxylase deficiency but no correlation was found between glucocorticoid dosage and BMD z-scores. Although patients with CAH received long term glucocorticoid treatment, their BMD z-score were similar to healthy controls.

This may be attributed to higher BMI z-scores and increased androgen levels in this population.
Cushing disease by ectopic ACTH in a child with esthesioneuroblastoma

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Cushing Syndrome (CS) by ectopic ACTH syndrome (EAS) is extremely rare among children, occurring much less frequently than its approximate 15% prevalence in adult ACTH-dependent CS. We describe a case of EAS in a male child, who had previous (11 months old) surgical resection of a large tumour localised in the nasopharynx and with intracranial extension. Histologically the neoplasia was consistent with the diagnosis of esthesioneuroblastoma (ENB). At the first endocrinological observation (2.8 yrs old) the child presented a typical CS phenotype; auxological evaluation showed short stature (-2.0 sds), with a very low height velocity and marked obesity (BMI: +6.8 sds). Endocrine examinations showed elevated 24h urinary free cortisol (UFC), elevated plasma levels of cortisol and normal levels of ACTH. Cortisol and ACTH levels showed both lack of circadian rhythm, non-suppressibility to high-dose dexamethasone test, and non-responsiveness to CRH test. Magnetic resonance imaging (MRI) of the pituitary, and Computerised Tomography (CT) of the chest and abdomen were negative. MRI maxillar-facial showed a relapse of the expansive lesion in right parafaringean region, that was treated with surgery, and local fractionated radiotherapy (41.4 Gy). At the last visit, at the age of 4.3 years, his auxological features were strong improved (height-sds: -1.1; BMI-sds: +0.2). He was healthy, without any hormonal problems.

Conclusions: the diagnosis EAS suspected on clinical findings was confirmed by cortisol elevation and absent ACTH and cortisol circadian rhythm and by dynamic tests. It was very difficult to localise the site of ectopic ACTH secretion by ENB. At present and for our knowledge of the literature the described boy is the first case of EAS consequent on ENB reported in paediatric age.

Effect of prednisone therapy on adrenal function, bone density and body composition in prepubertal children with duchenne dystrophy: A prospective study

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It is known that prolonged glucocorticoid therapy may lead several side effects such as osteoporosis and secondary hypoadrenalism. Prednisone is used commonly in patients affected by Duchenne muscular dystrophy (DMD) to improve and prolong ambulation, upper limb function and pulmonary function, and to delay walking loss and avoid spinal surgery. This therapy has to be administered for long period and therefore bone density and adrenal function can be affected in DMD children. In this study we evaluated the effect of intermittent therapy with prednisone (PDN) on adrenal function, bone mineral density (BMD) and body composition in DMD children. Twenty-six consecutive DMD ambulant children (mean age at baseline 4.8±1.5 yrs; Tanner stage 1) seen in our department between 2002 and 2008 were recruited before starting therapy with steroids. ACTH (0.25 mg iv) stimulation test, lumbar spine and whole body (WB) DXA scan were performed at diagnosis and after 12-24-36-48 months of PDN (10 days of therapy every other 10 days; standard dose of 0.75 mg/Kg/d). Our preliminary results showed that basal and ACTH stimulated plasma cortisol response was not impaired at 12 months (n=21), 24 moths (n=9), 36 months (n=6) and 48 months (n=3) of observation after the beginning of the therapy. Apparent lumbar BMD (aBMD), volumetric lumbar BMD (vBMD), lumbar Z score such as whole body BMD (wbBMD) and high normalized wbBMD did not statistically differ during the follow up period. Although not statistically significant, a tendency towards a mean increase of SD-BMI was observed in all pts but with no change in body composition (percentage of fat and lean mass at DXA scan). In conclusion adrenal function, BMD and body composition in DMD children do not seem to be significantly affected by long term treatment with intermittent low dose of PDN.
P2-d2-476 Adrenal 2
Sympathoadrenal function in children with premature adrenarche
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Premature adrenarche (PA) refers to an early increase in adrenocortical an-
drogen production leading to prepubertal hyperandrogenic signs, and it has
been associated with metabolic disturbances in some populations. As adrenal
medulla and cortex are known to interact, the aim of the present study was
to test the hypothesis that adrenomedullary function is altered in PA. We ex-
amined 73 consecutive prepubertal children with PA and 98 healthy age-
and gender matched control children at the median age of 7.5 years. The inclusion
criteria of the PA group included any of the following sign(s) before 8/9 years
of age (girls/boys, respectively): pubic/axillary hair, oily skin/hair, adult type
body odor. Birth weight (BW) and current BMI SDS were recorded, plasma
catecholamine and triglyceride, and serum DHEAS concentrations were
measured, and a standard oral glucose tolerance test (OGTT) with insulin
measurements was performed. Independent samples T-test, Mann-Whitney
test and Pearson’s correlation test were used for statistical analyses. Child-
ren with PA had similar plasma epinephrine (mean [SD] 0.22 [0.11] vs. 0.23
[0.17] nmol/L, P=0.90) but higher norepinephrine (NE) concentrations than
their controls (1.61 [0.70] vs. 1.39 [0.48] nmol/L, P=0.03). In the PA children,
NE concentration did not correlate significantly with BW SDS, current BMI
SDS, age or DHEAS concentration. However, the PA children with NE in the
highest quartile had lower BW SDS (-0.32 vs. +0.33, P=0.03), higher plasma
glucocorticoid dose in A compared to B at 6-10 years. In prepubertal years
(-2.64 and -1.81 SD). Most height loss occurred after the age of 10 years. The
corrected MPH and current BMI SDS were recorded. Urine steroidprofile (GCMS,
Groningen=A) or 17OHP/AD in saliva were used to determine which dose should be adjusted. Retrospectively, data of 31 patients from
a subgroup, MPH corrected of glucocorticoid, glucocorticoid dose, or division of the dose during the day. Possibly the difference in monitoring on urine or saliva might play a role. In
in patients with CAH due to 21-hydroxylase deficiency final height is below
target height. Linear growth, bone age, serum or saliva 17 α-oxysterone
(17OHP) and androstenedione (AD) or its urinary derivates are moni-
tored to optimize glucocorticoid substitution. We compared two ways of mo-
nitoring, urine steroidprofile (GCMS, Groningen=A) or 17OHP/AD in saliva
(Nijmegen=B). Center A aimed for normal pregnenolol/creatinine ratios
B for normal saliva AD concentrations. Urine or saliva data were used to de-
cide which dose should be used. Using different methods, data of 31 patients from
A and 74 from B were investigated for differences in glucocorticoid dose and
growth pattern at age 4-10 years. In the age interval 6-8 and 8-10, but not 4-6
years, mean glucocorticoid dose was higher in A than B (p=0.01), in parallel
with more cortisone acetate use than hydrocortisone. Children from both cen-
ters were small compared to the Dutch population. Growth retardation already
existed at 4 years. Height z-scores were not significantly different. Midpa-
renchal height (MPH) corrected height was significantly smaller at 8 years in A
than B (p=0.041) but comparable at 6 and 10 years. Multiple regression
showed no significant association between MPH corrected height and type
of glucocorticoid, glucocorticoid dose, or division of the dose during the day.
Possible difference in monitoring on urine or saliva might play a role. In
a subgroup, MPH corrected of glucocorticoid, glucocorticoid dose, or division of the dose during the day. Possibly the difference in monitoring on urine or saliva might play a role. In

P2-d2-480 Adrenal 2
Transient neonatal elevation of 17-OHP levels
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Background: Neonatal screening for congenital adrenal hyperplasia (CAH) is characterized by a high false-positive rate, mainly related to the hetero-
genicity of CAH clinical presentations.

Objective: The aims of our study were: to identify clinically, biochemically and by genotyping a subgroup of infants with transient serum hyper-17-hy-
droxyprogesteronemia and to compare those with false positive newborns and neones affected by 21-hydroxylase deficiency, all seen at our centre.

Methods: We retrospectively analyzed clinical data of all newborns positive at CAH neonatal screening from 2002 to 2006. They were submitted to
clinical investigations and blood tests to evaluate 17-hydroxyprogesterone (17-OHP), renin and electrolyte levels. In addition, serum measurements of
androstenedione, testosterone, ACTH, DHEAS, urinary electrolytes were per-
formed in almost all infants. All CAH-unaffected newborns with increased serum 17-OHP in comparison to normal levels for age were submitted to strict
follow-up monitoring, which included an ACTH stimulating test and genetic analysis of the 21-hydroxylase gene, until serum 17-OHP was normalized.

Results: Over the 5-year period, 38 newborns with gestational ages ranging from 33 to 41 weeks tested positive at CAH neonatal screening. Nine
infants (3M, 6F) were affected by CAH (serum 17-OHP: 96[70-307] ng/mL), 14 (10M, 4F) were false positives at CAH screening (17-OHP: 1.25[0.8-2.8]
ng/mL) and 15 (10M, 5F) showed a serum hyper-17-OHPemia (17-OHP: 5.3[3.3-11] ng/mL). Infants with hyper-17-OHPemia presented an elevation of
androgens levels with normal values of renin, ACTH, serum and urinary electrolytes. No mutations of the 21-hydroxylase gene were found in these
infants and their serum 17-OHP levels were normalized by the sixth month of

Conclusion: We identified a particular population of transient hyper-17-OH-
Plasma newborns and suggested a strict clinical follow-up of these infants until their serum levels were normalized. Further investigations might be ne-
necessary in childhood for the early detection of signs of hyperandrogenism.

P2-d2-478 Adrenal 2
Neonatal screening of congenital adrenal hyperplasia (CAH) in our area: Experience and 17-hydroxyprogesterone cutoff levels adjusted for birth weight and gestational age
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1Hospital Universitario Miguel Servet, Clinical Biochemistry, Zaragoza, Spain; 2Hospital Universitario Miguel Servet, Pediatric Endocrinology, Zaragoza, Spain

CAH due to 21-hydroxylase deficiency can be detected by neonatal screening
determination of 17-hydroxyprogesterone (17OHP) in filter-paper blood. The objectives are to study the prevalence of CAH in our population and to define
17OHP cutoff levels based on weight (BW) and gestational age (GA).

Patients and Methods: 44.403 newborns (March 2003 to December 2007). 17-OHP determination: solid-phase time-resolved fluorescent assay meth-
Two different cutoffs were used: 30 nmol/L (term newborns) and 50 nmol/L (preterm newborns). Results: 4 CAH cases were detected (1:11.101); 3 cases of salt wasting (SW) and 1 case of 21-hydroxylase deficiency (1:14.801) and 1 case of 3α-hydroxysteroid dehydro-
genase deficiency (1:14.403). 17OHP levels were adjusted for birth weight
(BW) and gestational age (GA) being significantly different among groups
(p<0.01).

P2-d2-479 Adrenal 2
Congenital adrenal hyperplasia and glucocorticoid monitoring
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1University Medical Center Groningen, Pediatric Endocrinology, Groningen, Netherlands; 2University Medical Center St. Radboud, Pediatric Endocrinology, Nijmegen, Netherlands

In patients with CAH due to 21-hydroxylase deficiency final height is below
target height. Linear growth, bone age, serum or saliva 17 α-oxysterone
(17OHP) and androstenedione (AD) or its urinary derivates are moni-
tored to optimize glucocorticoid substitution. We compared two ways of mo-
nitoring, urine steroidprofile (GCMS, Groningen=A) or 17OHP/AD in saliva
(Nijmegen=B). Center A aimed for normal pregnenolol/creatinine ratios
B for normal saliva AD concentrations. Urine or saliva data were used to de-
cide which dose should be adjusted. Retrospectively, data of 31 patients from
A and 74 from B were investigated for differences in glucocorticoid dose and
growth pattern at age 4-10 years. In the age interval 6-8 and 8-10, but not 4-6
years, mean glucocorticoid dose was higher in A than B (p<0.01), in parallel
with more cortisone acetate use than hydrocortisone. Children from both cen-
ters were small compared to the Dutch population. Growth retardation already
existed at 4 years. Height z-scores were not significantly different. Midpa-
renchal height (MPH) corrected height was significantly smaller at 8 years in A
than B (p=0.041) but comparable at 6 and 10 years. Multiple regression
showed no significant association between MPH corrected height and type
of glucocorticoid, glucocorticoid dose, or division of the dose during the day.
Possibly the difference in monitoring on urine or saliva might play a role. In
a subgroup, MPH corrected final height was significantly smaller in A than B
(-2.64 and -1.81 SD). Most height loss occurred after the age of 10 years. The
way of monitoring the glucocorticoid dose may have played a role in the
higher glucocorticoid dose in A compared to B at 6-10 years. In prepubertal years
growth pattern in A and B were largely comparable. Both groups lost height,
mainly occurring after the age of 10 years and more in A than B.
The goal of the present communication is to describe clinical characteristics of patients referred to two secondary hospitals for premature pubarche during the last 2 years.

Conclusions: Prevalence of CAH is in agreement with worldwide experience and the efficiency of programme can be substantially improved by using cutoff levels adjusted for BW and GA.

Introduction: Premature pubarche (PP) is the main manifestation of premature adrenarche. Nevertheless a differential diagnosis and follow up of the patients is needed.

Objective: To describe clinical characteristics of patients referred to two secondary hospitals for premature pubarche during the last 12 years.

Results: 95 cases of PP were examined (16 boys), three girls had also clitoromegaly. Three cases had maternal history of polycystic ovarian syndrome. Concomitant perivascular and small focal hemorrhages. The adrenal cortical layer is represented by thin medullar layers in the form of strands, basophilic cells folding in trabecular structures, with plethoric capillary network and occasional perivascular and small focal hemorrhages. The adrenal cortical layer is completely absent and the adrenal connective tissue capsule covers directly the medullar layers. Cells of paranephral adipose tissue are hypoatrophied. The medullar layers are directed for histological examination. Morphologically, the adrenals are diagnosed as the same disease. We performed mutation analysis in two sisters by the cortical layer atrophy, the medullar layer hypoplasia, and perivascular and the efficiency of programme can be substantially improved by using cutoff levels adjusted for BW and GA.

Conclusions: In most instances, treatment is not indicated in PP. Follow-up is recommended in order to know final height and because it has been associated with hyperinsulinism, dyslipidemia, obesity and polycystic ovarian syndrome in adolescents.

When cutoff levels adjusted for BW and GA were used the total false positive rate was reduced from 9.2% to 1.4%; low birth weight and preterm newborns showed significantly higher improvement.

Background: The triple A syndrome (Allgrove syndrome) is a rare autosomal recessive disorder characterized by association of adrenal deficiency, achalasia, alacrimia, and variety of neurological and dermatological features. The adrenal insufficiency is due to resistance to ACTH and is manifested as a rule as deficit of glucocorticoids. Only about 10% of patients with this disease have mineralocorticoid deficiency.

Objective and Hypotheses: The goal of the present communication is to describe pathomorphological changes in adrenals in a child with Allgrove syndrome.

Population and/or Methods: We observed a 13-year old boy with Allgrove syndrome who had glucocorticoid and mineralocorticoid deficiency, palmarplantar hyperkeratosis, epilepsy, and partial optic atrophy. The patient was treated with hydrocortisone 10 mg/day, fludrocortisone 0.05 mg/day, and sodium valproate 200 mg/day. At the age of 15 years, he suddenly died in the morning. The child had no symptoms of any diseases not connected with Allgrove syndrome. Tentatively the cause of the lethal outcome was an attack of epilepsy.

Results: Adrenals are not revealed visually; the para-adenal adipose tissue is directed for histological examination. Morphologically, the adrenals are represented by thin medullar layers in the form of strands, basophilic cells folding in trabecular structures, with plethoric capillary network and occasional perivascular and small focal hemorrhages. The adrenal cortical layer is completely absent and the adrenal connective tissue capsule covers directly the medullar layers. Cells of paranephral adipose tissue are hypoatrophied. The medullar layers are directed for histological examination. Morphologically, the adrenals are diagnosed as the same disease. We performed mutation analysis in two sisters by the cortical layer atrophy, the medullar layer hypoplasia, and perivascular and small focal hemorrhages in the hypoplastic medullar layer.

Conclusions:

CYP21A2 gene.

c.1136_1137del(p.Pro379ArgfsX16) in combination with gene conversion of CYP21A2 gene, which is a novel mutation. Their mother was a carrier of the CYP21A2 gene. Rearrangements with pseudogene (CYP21A1) were analyzed by PCR using cross-primers. Two sisters were compound heterozygotes for c.329_336del, pseudogene derived CYP21A2 gene conversion. We report two Korean sisters with salt-wasting CAH due to a novel mutation of CYP21A2 gene, which is a novel mutation. Their mother was a carrier of c.329_336del, pseudogene derived CYP21A2 gene conversion. We report two Korean sisters with salt-wasting CAH due to a novel mutation of CYP21A2 gene in combination with gene conversion of CYP21A2 gene.

Conclusions: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of steroidogenesis most commonly caused by 21-hydroxylase deficiency due to mutations in CYP21 gene. We experienced two Korean sisters suffering from salt-wasting CAH, in whom a novel mutation of the CYP21 gene was detected. A female baby was born with ambiguous genitalia with clitoromegaly and dark pigmentation. Highly elevated 17-hydroxyprogesterone (840 ng/mL), increased plasma renin activity, hyperkalemia lead to the diagnosis of salt-wasting CAH. Her 6-year-old sister had been diagnosed as the same disease. We performed mutation analysis in two sisters and their parents by direct DNA sequencing after allele-specific PCR amplification of the CYP21A2 gene. Rearrangements with pseudogene (CYP21A1) were analyzed by PCR using cross-primer. Two sisters were compound heterozygotes for c.1136_1137del(p.Pro379ArgfsX16)c.329_336del(p.Gly111_Tyr113delinsVal5fsX31). Their father was a carrier of c.1136_1137del of CYP21A2 gene, which is a novel mutation. Their mother was a carrier of c.329_336del, pseudogene derived CYP21A2 gene conversion. We report two Korean sisters with salt-wasting CAH due to a novel mutation of c.1136_1137del(p.Pro379ArgfsX16) in combination with gene conversion of CYP21A2 gene.

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Conclusions: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of steroidogenesis most commonly caused by 21-hydroxylase deficiency due to mutations in CYP21 gene. We experienced two Korean sisters suffering from salt-wasting CAH, in whom a novel mutation of the CYP21 gene was detected. A female baby was born with ambiguous genitalia with clitoromegaly and dark pigmentation. Highly elevated 17-hydroxyprogesterone (840 ng/mL), increased plasma renin activity, hyperkalemia lead to the diagnosis of salt-wasting CAH. Her 6-year-old sister had been diagnosed as the same disease. We performed mutation analysis in two sisters and their parents by direct DNA sequencing after allele-specific PCR amplification of the CYP21A2 gene. Rearrangements with pseudogene (CYP21A1) were analyzed by PCR using cross-primer. Two sisters were compound heterozygotes for c.1136_1137del(p.Pro379ArgfsX16)c.329_336del(p.Gly111_Tyr113delinsVal5fsX31). Their father was a carrier of c.1136_1137del of CYP21A2 gene, which is a novel mutation. Their mother was a carrier of c.329_336del, pseudogene derived CYP21A2 gene conversion. We report two Korean sisters with salt-wasting CAH due to a novel mutation of c.1136_1137del(p.Pro379ArgfsX16) in combination with gene conversion of CYP21A2 gene.
Variables related to behavioral and emotional problems and gender typed behaviors in female patients with congenital adrenal hyperplasia

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Background: The determinants of the psychological consequences of congenital adrenal hyperplasia need to be investigated in more detail.

Objective: In this study, we aimed to investigate the effects of congenital adrenal hyperplasia (CAH) type, treatment, endocrinological, surgical, and sociodemographic factors as well as patients’ body perception on the gender-typed play and behavioral and emotional problems in female children with CAH.

Method: The sample included 28 females with CAH (age mean: 12.6 years, sd:3.9, range 8-20). In order to control the psycho-social stress related to chronic disorder, we compared patients with CAH to 28 age matched patients with type 1 diabetes mellitus (DM, age mean: 12.5 years, sd:3.9) and healthy controls (age mean: 12.8 years, sd:3.7). Seven of 147 patients (4.8%) had a history of low birthweight. One hundred and sixty,56ug/l) Blood level of Chromogranine A were within normal limits (range 31,8 -110ng/l)

Metanephrine: 7,611ng/l (range 0,1-30,422ng/l)

Results: Patients with CAH had significantly higher externalization and total problems scores obtained from parent and teacher ratings. Even none of the patients diagnosed as having gender identity disorder patients with CAH had less interest in gender role behaviors. The multiple regression analysis revealed that the behavioral and emotional problems in patients with CAH were associated with the patients satisfaction with the appearance of their genitalia, the surgeons’ assessment of the success of the surgical procedures, and mean testosteron level of the patients.

Conclusions: Our results showed that CAH patients were reported to have higher behavioral and emotional problems both in home and at school. The CAH group also had less gender typed behaviors. Severity of the behavioral and emotional problems were associated with severity of androgenization (e.g. mean testosterone level), patients perception of their genitalia and the surgical outcome.

P2-d2-487 Adrenal 2

Prenatal diagnosis and treatment of congenital adrenal hyperplasia: Our experience

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Prenatal diagnosis and treatment for fetuses at risk for classical Congenital Adrenal Hyperplasia (CAH) has been used in the last decades to prevent genital virilization of female affected fetuses; however some ethical aspects and long-term outcome are still controversial. We describe four cases of prenatal diagnosis with different outcomes. The four cases occurred in families with a previously affected sibling in whom genotyping of the proband and parents had been performed. Pregnant mothers were treated with dexamethasone 20 mcg/kg/day, starting between the 5th and the 8th wks GA. Genetic analysis on chorionic villous samples diagnosed classic CAH in one male (omoizous 12 splice) and in one female (12/R479L) fetuses; two fetuses were not affected females. Treatment was discontinued at 12th -13th wks GA in the two non affected and in the affected male fetuses. The affected male was delivered by Cesarean section at 39 wk GA; weight was 3650 gr; length was 51 cm; head circumference 35 cm; no malformations were present. At 1 week of age treatment with hydrocortisone, fludrocortisone and NaCl supplement was started. He is currently under follow-up. The mother of the affected female decided for an elective abortion although at the beginning of pregnancy she had been adequately informed about the significance of the treatment and about its role in preventing genital virilation. The affected child of this mother was a girl, born with ambiguous genitalia. Her decision showed that coping with the disease of her child had been more difficult and stressfull than medical team had perceived. The treated pregnant mothers did not experienced side effects. In conclusion, our experience highlighted two issues in CAH management: i) the ethical concern in treating non affected fetuses (seven out of eight) with a treatment which long-term effects are not yet completely clarified; ii) the negative psychological impact of the child disease on parents may be present to a greater degree than appears, and needs to be accurately investigated and adequately supported.

P2-d2-488 Adrenal 2

Is ACTH stimulation test essential for all cases with premature adrenarche?

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Premature adrenarche (PA) may be a manifestation of late onset congenital adrenal hyperplasia (CAH). Controversy exists as to whether all children with PA should undergo an ACTH stimulation test. To assess the frequency of late onset CAH among the population with PA, and to define the clinical and laboratory criteria indicating an ACTH stimulation test in such patients. We retrospectively analyzed 147 prepubertal patients (125 girls) who had prepubertic pubic or axillary hair development (before 8 years in girls and 9 years in boys). Auxological parameters and basal (b) and stimulated (s) 17OHPP, 11-deoxy cortisol (11-DOC) levels in ACTH stimulation test (Synacthen, 0.25 mg iv) were analyzed. Patients with a s17OHPP above 10 ng/ml were considered as late onset CAH. Mean for age at admission was 7.3±1.1 years; age at onset of complaint was 6.5±1.0 years; bone age was 8.3±1.4 years; BMI SDS was 1.09±1.16 SDS; height SDS was 1.02±1 SDS. Seven of 147 patients (4.8%) had a history of low birthweight. One hundred and twelve patients with b17OHPP level  5 ng/ml. Two of them had s17OHPP level 10-15 ng/ml and 2 of them had 15 ng/ml. None of the patients had elevated 11-DOC levels. Clinical findings regarding age at onset, BMI SDS, height SDS and bone age SDS did not differ among groups with different s17OHPP levels (s17OHPP: <5 ng/ml, 5-10 ng/ml, 10-15 ng/ml, >15 ng/ml). The frequency of late onset CAH with ACTH stimulation test was 4% among the patients with PA. ACTH test is not essential in patients with PA who had b17OHPP levels 2-5 ng/ml regardless of clinical findings.

P2-d2-489 Adrenal 2

Congenital adrenal hyperplasia and function of adrenal medulla

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Aim: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from deficiency of enzymes important for synthesis of glucocorticoids (cortisol) and often mineralocorticoids in cortex of adrenal gland. The most frequent form is caused by deficiency of 21-hydroxylase and mutation of CYP gene. Three clinical forms are known: classical salt-wasting, classical simple virilizing and nonclassical form. The salt-wasting form with possible development of adrenal crisis (polyuria, natriuria, dehydration, hyponatremia, hyperkalemia) is the most severe form.

Material and Methods: Thirty-seven patients with salt-wasting form CAH were followed-17 male, 20 female, age range 5-40 years. All these patients were treated with hydrocortisone 10-19mg/m2/d three times daily and 9-alfa fludrocortisone 50-100ug/d twice daily.

Results: The blood levels of cortisol, 17-hydroxyprogesterone, testosteron and androstendione were in normal limits. The mean blood levels of free metanephrine, normetanephrine and chromogranine A in our patients were as follow: Metanephrine: 7.611ng/l (range 0,1-30,422ng/l) versus normal level 50,000ng/l (range 10-100ng/l) Normetanephrine: 19.936ng/l (range 0,1-90,722ng/l) versus normal level 92,500ng/l (range 15-170 ng/l) Blood level of Chromogranine A were within normal limits (range 31,8 - 136,56ug/l) Authors didn’t find difference between males and females and between children and adults.
Conclusions: The low level of metanephrine and normetanephrine can encourage diagnosis of salt-wasting form CAH and the severity of disease.

P2-d2-489 Adrenal 2
Phenotype and genotype in CAH patients
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Background: CAH is a family of inherited disorders of adrenal steroidogenesis resulting from a deficiency in one of the five enzymatic steps necessary for normal cortisol synthesis. CAH occurs in about 1:3000-1:23000 live births. More than 95% of CAH cases are caused by 21-hydroxylase deficiency that presented in two forms: classic form including saltwasting and simple virilizing form and non classic form. Others types are 11-hydroxylase deficiency (11-OH) occurs in %5-8, 3B-HSD and 17-hydroxylase deficiency (17-OH) less than %.1. This types can produce ambiguity in males and females.

Objective: To determine the phenotype and genotype in CAH patients.

Method: This cross-sectional study was conducted in 2003-2005 in Aliasgar hospital in Tehran of Iran. 156 patients with CAH were selected randomly. Demographic data were collected by questioner. Physical exam for ambiguous genitalia and laboratory tests consist of 17-OHP, serum Na, K, Renin and aldosterone done by specialist. Data were processed by SPSS software and analyzed by descriptive statistics.

Results: Of 156 patients, 87(%55.5) were female. 21-OH was reported in 118 ones (%75.7) which 70 ones were with ambiguous genitalia and 48 were male. Then the most common forms were 11-OH (15.1), 3B-HSD (17.1) and 17-OH deficiency (3.2) respectively. Most of them (105 ones) had salt wasting form (female/male ratio was 61 to 44). According to prader grading (0 to 5) ambiguity assessed in 40 ones.

Conclusion: CAH prevalence is relatively high in our country because of consanguinity. Ambiguous genitalia needs many surgery to repair and adrenal crises has high mortality especially in boys with salt wasting phenotypes. So, early prenatal diagnosis and postnatal screening would be helpful.

P2-d2-490 Adrenal 2
Comparison of low dose and high dose cosyntropin stimulation tests in healthy short children and in children with an impaired hypothalamic-pituitary axis
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The Cosyntropin stimulation test is used to screen for secondary or tertiary adrenal insufficiency. Studies suggest that standard high dose (250 micrograms, HD) is supra-physiologic and low dose (1 mcg, LD) is more reliable. The objective of this study was to determine the reliability of LD versus HD Cosyntropin stimulation testing in evaluating the hypothalamic-pituitary-adrenal axis (HPA) in children. Charts from patients receiving intravenous LD (1 mcg) and HD (249 mcg) Cosyntropin consecutively while undergoing growth hormone stimulation testing during the past year were reviewed. Baseline, 30° and 60° cortisol levels were obtained following LD Cosyntropin and baseline, 30° and 60° following HD Cosyntropin. Thirty seven patients were included. Patients who passed GH stimulation testing and were not on oral, inhaled or intranasal steroids comprised group A (n: 20, intact HPA) and children who failed GH stimulation testing and/or who were on oral, inhaled or intranasal steroids comprised group B (n:17, impaired HPA). The mean baseline cortisol level in group A was 10.6±4.1 mcg/dL and in group B was 8.1±5.5 mcg/dL. The mean peak cortisol level in group A after LD Cosyntropin was 18.8±2.6 mcg/dL and after HD Cosyntropin was 25.2±3.1 mcg/dL (p<0.05). The mean peak cortisol level in group B after LD Cosyntropin was 15.7±6.1 mcg/dL and after HD was 21.7±7.9 mcg/dL (p<0.05). In group A, 48% would have been misdiagnosed with central adrenal insufficiency if a peak cortisol level of >18 mcg/dL was used as the normal cut-off as previously published. The response to LD and HD Cosyntropin stimulation testing seems to be different both in children with intact and impaired HPA and the recommended cut-off for normal cortisol response in LD Cosyntropin stimulation testing should be lowered to > 14 mcg/dL.

P2-d2-491 Others
Endocrine complications after hematopoietic stem cell transplantation during childhood and adolescence
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Long-term survivors after hematopoietic stem cell transplantation (HSCT) in childhood and adolescence are at risk of developing endocrine complications. The purpose of this study was to investigate long-term endocrine complications and their risk factors among patients who underwent HSCT during childhood and adolescence. We analyzed clinical and laboratory data of one hundred fourteen patients (61 males and 53 females) who were treated with HSCT at the mean age of 8.6±4.6 years. Growth markers, pituitary and thyroid hormones, lipid profiles, bone age and/or pelvic ultrasonogram were evaluated. Thirty-one patients (27.2%) showed growth retardation, and six (5.3%) of them had growth hormone deficiency. The risk of growth retardation was higher in males (39.3% vs 13.2%, P<0.05) and patients with younger age at HSCT (P<0.05). Twenty-nine patients (25.4%) developed hypothyroidism, and twenty of them were categorized as compensated hypothyroidism. The risk of low TSH was higher in patients treated with total body irradiation (TBI)-based regimen (33.9% vs 16.4%, P<0.05). Nineteen males (31.1%) and 27 females (50.0%) were hypogonadic. The risk of gonadal dysfunction was higher in females (P<0.05), patients treated with TBI-based regimen (46.9% vs 31.4%, P<0.05), and those with older age at HSCT (P<0.05). Four patients (3.5%) were obese, and 19 (16.7%) had abnormal lipid profiles. These results suggest that the majority of patients who underwent HSCT during childhood and adolescence have one or more endocrine complications and that anticipatory long-term monitoring is necessary.

P2-d2-492 Others
Hypomagnesemia with secondary hypocalcemia due to a frameshift mutation in TRPM6
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Case Report: Herein, we report a 17-year-old female of Lebanese descent born to consanguineous parents who presented at one month of age with seizures secondary to hypocalcemia. At that time she was also found to have hypomagnesemia. This resulted in replacement therapy with magnesium and calcitriol. She had persistently low magnesium but normal calcium levels. PTH levels were low on some occasions. Over the next few years, she developed florid dental caries with enamel dysplasia and complained of numbness in her feet and legs despite being on replacement therapy. A renal ultrasound showed normal kidneys with no nephrocalcinosis. The patient has a sibling who presented at 15 days of age with similar symptoms. The sibling was initially treated with Valium in Lebanon thus presenting with profound short stature and mental retardation at the clinic.

Results: DNA analysis by SSCP yielded a band shift in exon 4 in parents, patient and her sibling. Subsequent sequencing of the coding sequence and adjacent intronic boundaries showed a homozygous deletion of a cytosine residue at position 318 of the TRPM6 coding sequence leading to a shift of reading frame translation and a complete loss of function of the TRPM6 protein.

Discussion: Familial hypomagnesia with secondary hypocalcemia can be caused by a defect in the small intestines causing hypocalcemic tetany or seizures at age 2-3 weeks. This is a rare autosomal recessive that can be caused by various mutations. TRPM6 is expressed mainly in the gastrointestinal tract as well as in the kidney’s predominantly in the distal convulated tubules where it is presumed to be involved in the apical entry of magnesium into epithelial cells. The above patient, born from consanguineous parents has a sibling with similar symptoms.
Adrenoleukodystrophy/Adrenomyeloneuropathy (ALD/AMN) is an X-linked disorder of peroxynzymal metabolism of very long chain fatty acid (VLCAFA) associated with Central Nervous System (CNS) demyelination, adrenocortical insufficiency and hypogonadism. It was already demonstrated that oxidative stress is involved in the pathophysiology of neuropathy of X-ALD/AMN and that the total antioxidant defenses were decreased in symptomatic patients (pts). We show the results of a crossover double blinded study on 24 X-ALD/AMN symptomatic pts (20 males and 4 females; age 20-57 years) randomized to alpha lipoic acid (1200 mg/daily per os) or placebo treatment. Out of 24 pts 17 were on hydrocortison, 11 on Lorenzo’s oil and 7 on statin. Clinical, biochemical, and hormonal assessment were performed every four months. The Karnofsky Performance Scale Index that allows patients to be classified as to their functional impairment and endocrine assessment (ENG) were completed every four months before and after pts received drug or placebo. We did not find any significant difference for all the parameters studied. Biochemical and hormonal data were not statistically changed during the study. No statistical differences in Karnofsky score and in the motor and sensory conduction of the median, radial, sciatic and sural nerves evaluated with ENG were detected. Our results suggest that alpha lipoic acid, a potent antioxidant, does not improve symptoms and neurodegeneration in pts affected by X-ALD/AMN, although larger studies with different doses of the drug and longer follow up are needed.

A prospective randomized double blinded study with alpha lipoic acid in adrenoleukodystrophy
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Acanthosis nigricans and insulin sensitivity in patients with skeletal dysplasia
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Achondroplasia is an autosomal dominant skeletal dysplasia affecting approximately 1:15,000 to 1:40,000 live births, caused by activating mutations in FGFR3. Activating mutations in FGFR3 may also cause hypochondroplasia and are responsible for severe skeletal dysplasias associated with acanthosis nigricans (AN), such as thanatophoric dysplasia, severe achondroplasia with developmental delay and AN (SADDAN syndrome) and Crouzon syndrome with AN (A391E, K650M). We report five male patients, four with achondroplasia [P1-P4] who had the common G380R mutation and one with hypochondroplasia [P5] due to the N540K mutation, who developed AN without SADDAN and compare the results of a 1.75g/kg oral glucose tolerance test (OGTT) with 5 age, sex and pubertal matched short children. Patients’ characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
</tr>
</thead>
<tbody>
<tr>
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<td>13.1</td>
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<tr>
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<td>122.8</td>
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<td>Weight (kg)</td>
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<td>59.3</td>
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<tr>
<td>Fasting Plasma Glucose (mmol/l)</td>
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<td>4.4</td>
<td>4.3</td>
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<tr>
<td>GH therapy at time of study</td>
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<td>Yes</td>
<td>No</td>
<td>Stopped</td>
</tr>
</tbody>
</table>

Three of the patients were treated with rGH (dose range 25-30U/m²/week), one patient had discontinued treatment, and one had never been treated. Body mass index was higher in the achondroplastic patients (28.9±7.3 kg/m², range 22-39.3kg/m²). Mean fasting plasma insulin was greater in the controls compared to those with achondroplasia (13.3mU/l vs 6.2mU/l, p=0.03), as was HOMA1-IR (2.9 vs 1.2 p=0.04). There was no significant difference in mean peak insulin concentration (113.7mU/l vs 120.0mU/l, p=0.73) nor in mean plasma glucose concentration at 120min (5.6mU/l vs 6.0mU/l p=0.75). No patient had plasma glucose more than 7.8mmol/l at 2 hours. These findings suggest that AN in achondroplasia is not due to insulin insensitivity either on its own or secondary to Growth Hormone treatment; whether it is due to altered melanocyte function in these individuals remains to be established.

CIMT and markers of endothelial function in adolescents with increased risk for vascular complication
Metaile Ehirmiotou1; Zeynep Alev Ozon1; Rahsan Gocmen2
1Ihsan Doðramaci Children Hospital, Pediatric Endocrinology Department, Ankara, Turkey; 2Ihsan Doðramaci Children Hospital, Radiology Department, Ankara, Turkey

Atherosclerosis, considered to be an adult disease, is now thought to have its onset in early childhood. Endothelial dysfunction is the first step in its pathogenesis. Obesity and hyperglycemia are two important risk factors for atherosclerosis. Carotid artery intima media thickness (CIMT) may provide information about early changes in the arterial wall during the subclinical stage. In this study we aimed to analyze early onset changes in adolescents with risk of atherosclerosis (obesity with or without glucose intolerance and type 1 DM) in comparison to healthy controls using CIMT and plasma levels of markers for endothelial function. Children over 10 years considered to carry risk for vascular disease such as obesity, type 1 DM, and obesity associated with glucose intolerance were included in the study. 20 children in each group were compared to 20 age, sex matched healthy controls. Mean CIMT was similar among patients and controls. Obese patients comprised 86% of the subjects with a CIMT in the upper quartile. Mean homocysteine level of subjects in the upper quartile for CIMT was higher than that of the lower quartile. Homocysteine was positively correlated to CIMT, and both folic acid and vitamin B12 levels were negatively correlated to homocysteine. There was no correlation between markers of endothelial dysfunction and CIMT. Mean CIMT was statistically higher in type 1 diabetes patients with microalbuminuria (0.43±0.06 mm) than those who were normoalbuminuric (0.37±0.05 mm). Findings suggest that obesity induced atherosclerosis may have its onset during childhood, and plasma homocysteine level may be an important risk factor for atherosclerosis. Folic acid and vitamin B12 supplementation may reduce this risk. Finally higher CIMT in type 1 diabetic patients with microvascular complications in comparison to normoalbuminuric patients needs further study, since current data involved few patients with complications.

Body composition chart as a screening tool for metabolic risk in children
Souchon Chung; Kyu-Sun Kim
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Background: Body mass index (BMI) change during childhood is not reflecting the exact change of adiposity level. Adequate acquisition of lean mass is crucial during growth. Furthermore inappropriate longing for leanness is an emerging social issue in adolescent girls, especially in Korea and undernutrition among children is still unresolved problem.

Objectives: The aims of this study were 1) to evaluate body composition change in children aged 8-12 years according to age and sex 2) to introduce the concept of body composition chart as a screening method of nutritional status.

Methods: Anthropometric measurement and body composition analysis was conducted in 965 school children 8 to 12 years of age (501 boys, 464 girls). Children were categorized, obese; overweight and control by percentage overweight based on the age- and sex-specific standard body weight for height. Fat mass index (FMI) and fat free mass index (FFMI) were calculated from anthropometric data. Finally higher CIMT in type 1 diabetic patients with microvascular complications in comparison to normoalbuminuric patients needs further study, since current data involved few patients with complications.

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weight; metabolic obese with normal weight and normal metabolism with normal weight. Most of the obese children and controls were plotted on obesity zone and normal metabolism with normal weight zone respectively. The starting of longing for leanness and possible metabolic inadequacy in teenage girls was demonstrated on body composition chart as plotted on the zone of metabolic obese with normal weight.

Conclusions: Body composition chart by age and sex should be developed as a screening tool in the assessment of nutritional status and metabolic risk in growing children.

**P2-d2-497 Others**

**Beta-endorphine levels in children with endocrine disturbances**

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**Background:** A few data of experiments indicate that opioids play an important role in behavior, appetite and hormonal secretion control. The data suggest neuro-modulatory role of endogenic opioids in GH secretion; the participation in glucose-homeostasis regulation processes and relation between opioid system and pituitary thyroid axis function.

**Materials:** 90 children, 10-17 years of age with endocrinological dysfunction: 20 children with GH deficiency - stature below 3 percentile, bone age delay (M=32% in comparison to chronological age); 30 children with IDDM (both in ketoacidosis state and during balance period); 30 children with hyperthyroidism and 10 children with hypothyroidism before and during treatment. The control group consisted with 30 healthy peers.

**Methods:** Beta-endorphin (β-E) levels (RIA Kit Incstar Corp.) were in those groups investigated.

**Results:** - E levels in healthy individuals was M= 8.43±1.41 pmol/l, in GH deficiency was M=6.02±2.05 pmol/l, in hyperthyroidism before and during treatment was M=8.77±2.57 and M=5.71±2.29 pmol/l, respectively; in hypothyroidism before and during treatment was M=5.5±1.20 pmol/l and M=10.57±1.92 pmol/l, respectively; in IDDM group with ketoacidosis was M=5.12±2.02 pmol/l and after achieving metabolic balance was 8.26±2.37 pmol/l.

**Conclusions:** In GH deficiency there was low levels of β-E. The lowest values are determined in children with bigger bone age delay. The changes of TSH and β-E levels during treatment of adolescents with hyper- and hypothroidism suggest the correlation between opioid system and thyroid activity. In diabetic children with ketoacidosis and increased fructosamine values - β-E levels were lower in children with normal fructosamine level and during balance period.

**P2-d2-498 Others**

**Elevated Ghrelin levels in preterm born children during prepubertal ages and relationship with catch up growth**

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**Background:** Ghrelin, the natural ligand of the GH secretagogue receptor, has potent orexigenic effect. Ghrelin levels are negatively associated with insulin secretion; increased in anorexia and reduced in obesity. Increased ghrelin levels may be associated with early postnatal growth in preterm born children.

**Objective:** Aim of this study was to evaluate ghrelin and insulin levels in preterm born children born appropriate for gestational age (AGA) or small for gestational age (SGA) and relations with catch up growth (CUG) at prepubertal ages.

**Methods:** 84 preterm born children grouped as premature SGA (n=28) and premature AGA (n=56) were evaluated at age 4.7±0.2 years and 4.7±0.1 years with respect to their ghrelin and insulin levels. Their data were compared to that of body mass index (BMI) matched term SGA (n=35) and term AGA (n=44) children of age 4.6±0.2 years and 4.5±0.1 years. All children had height appropriate for their target height. CUG was defined as the difference between birth size and recent size and expressed as Dheight and Dweight SDS.

**Results:** Preterm SGA and preterm AGA children had similar ghrelin levels (1717.0±166.9 pg/ml and 1656.5±103.8 pg/ml) although Dheight and Dweight SDS in preterm SGA were significantly higher than in preterm AGA children (p<0.001). Ghrelin levels in both preterm groups were higher than in term SGA (469.2±132.5 pg/ml) and in term AGA children (659.6±143.3 pg/ml) (p<0.001 for all). Dheight and Dweight SDS of the term SGA children were similar to that of preterm SGA children. Ghrelin did not have correlation with CUG but had inverse correlation with recent anthropometric indices. Insulin was significantly higher in term SGA children than in other groups (p<0.001).

**Conclusions:** Preterm children have higher ghrelin levels at prepubertal ages regardless of the magnitude of their CUG. Term SGA children, on the other hand, behave differently and have lower ghrelin levels than preterm children at prepubertal ages which may be related to elevated insulin levels in this group.

**P2-d2-499 Others**

**Clinical manifestations and endocrinologic disorders in Neurofibromatosis type 1 (NF1)**

Rosalba Bergamaschi; Laura Mazzanti; Emanuela Scarano; Laura Castiglioni; Francesca Montanari; Michele Torella; Franco Zappulla; Alessandro Cicogna

Department of Pediatrics, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

**Background:** NF1 is an autosomal dominant disorder sporadic in 50%. The NF1 gene, located on chromosome 17q11.2, is a large tumor suppressor gene that codes for a cytoplasmic protein: neurofibromin.

**Patients and Methods:** 87 patients (46 F and 41 M), diagnosed according to NIH, age at first examination 6 years, 50.5% familial cases, 49.5% sporadic.

**Results:** more than 6 cafe-au-lait spots 100%, 80% freckling, 20% Lisch nodules. Cutaneous neurofibromas in 43%, and plexiform neurofibromas in 8%. Scoliosis in 30%, macrocephaly in 50%. Optic pathway gliomas in 16%, average age of 3 yrs. Unidentified bright objects at brain MR in 54%. Mean stature at 35th pc, short stature (<10th pc) in 30%. Mean target height significantly lower in familial NF1 than sporadic cases (157 cm > 10th pc in females with familial form vs 161 cm > 25th pc in sporadic form; 170 cm > 10th pc in males with familial form vs 175 cm > 25th pc in sporadic forms). 15 pts showed NF1-Noonan syndrome condition, with stature significantly lower than NF1. Age of pubertal onset within the normal range in most patients, average age at menarche 12 years. Central precocious puberty (CPP) in 4 pts (4.5%), 2 females and 2 males, 3 with optic chiasma gliomas on MR. Growth hormone deficiency (GHD) in 7 pts (8%), 2 with optic chiasma glioma, 1 with both GHD and CPP, associated with glioma. Only 3 pts with CPP treated with LHRH analogues, recombiant human GH administered to 3 pts with GHD.

**Conclusions:** NF1 may lead to high degree cognitive, social and physical disability and necessitate a multidisciplinary approach. CPP and GHD are important complications. Although a glioma of the optic chiasm is often associated with this condition, CPP and GHD also appear in its absence therefore a careful follow-up is essential.

**P2-d2-500 Others**

**Environmental factors and blood pressure in pre-school children**

Agnieszka Ciszek; Anna Cieoalka; Anna Nowak; Magdalena Wirth; Ewa Barg

Wrocław Medical University, Endocrinology for Children and Adolescents, Wrocław, Poland

Hypertension is a civilization disease connected mainly with the lifestyle. The aim of the study was to estimate the impact of environmental factors on blood pressure in pre-school children. A two-step examination covered the group of 75 children, (40 girls and 35 boys), aged 2.5 to 6 (5,027±0,91). After carrying
out a questionnaire among the children's parents, antropometric and blood pressure measurements were performed. The children were divided into 2 groups: overweight (OO) (BMI ≥90c) and normal weight (NO). 35% children belong to group OO, mean BMI was 93.65±3.33 centy. The correlation between birth weight (r=0.281) and length (r=0.248) and current percentile of BMI was observed. Systolic, but not diastolic, blood pressure in group OO was statistically higher than in the NO group. A positive correlation between the circumference of children's waist (r=0.314) and hip (r=0.502) and the systolic blood pressure was observed, as well as negative correlations between the period of breastfeeding and the circumference of abdomen, hip and diastolic pressure (r=-0.265, r=-0.396, r=-0.270 respectively). The correlation between weight in the 2nd and the 4th year of life and the current BMI percentile (r2=0.376,r4=0.538), waist (r2=0.62,r4=0.586), hip circumference (r2=0.621,r4=0.703) and systolic pressure (r2=0.333,r4=0.637) was noticed.

Meals composition was observed to be related to the level of mothers' education. Children of mothers with higher education level eat less bread and fruit (r=-0.254, r=-0.277 respectively). 51% of the children eat sweets every day and a positive correlation between sweets and the circumference of abdomen (r=0.418) was stated. Children watch TV for 1,8±1.06h every day, but the overweight ones for 0,4h longer - a positive correlation between watching TV and waist/hip ratio (r=0.260) was observed. Only 9% of the children practise sport.

Conclusions: Hypertension is not only a problem of adults, but the lifestyle of preschoolers indicates a danger of a rising number of hypertension cases in children.

**P2-d2-501 Others**

**The plateau of urine osmolality in strict water restriction is pivotal in diagnosis of habitual polydipsia: Approaches of diagnosis in habitual polydipsia in infants**

Saiichiro Enkai1; Kalko Asto1; Daisuke Arisyasu1; Masako Izawa1; Junko Miyamoto1; Yukihiro Hasegawa1

1Tokyo Metropolitan Kiyose Children’s Hospital, Division of Endocrinology and Metabolism, Tokyo, Japan; 2Toho University Omori Medical Center, The First Department of Pediatrics, Tokyo, Japan

There have been few reports on diagnosis of patients with habitual polydipsia in infants. The diagnosis of habitual polydipsia is sometimes difficult because polyuria and polydipsia are also observed in patients with diabetes insipidus (DI). DDAVP therapy, which is necessary for DI, may induce water intoxication in patients with habitual polydipsia. Thus, it is important to diagnose patients with habitual polydipsia properly. The purpose of this study is to reveal appropriate approaches in diagnosis of habitual polydipsia in infants. The subjects were eight infants with habitual polydipsia. Water restriction test (WRT) was done with strict criteria of plateau urine osmolality; the plateau was defined when maximal change in urine osmolality in the four sequential samples was less than 100 mOsm/kg (EJ 38(5): 451-456, 1991). The diagnostic approaches of habitual polydipsia were investigated retrospectively. Three out of the eight cases were suspected to have habitual polydipsia in an outpatient clinic based on clinical histories and biochemical parameters. The diagnosis was confirmed after the three therapeutic procedures (reduction of amount of each fluid intake, discontinuation of infant-feeding bottles, and substitution of water for juice and barley tea) were successfully taken within four months. The other five cases had been misdiagnosed as DI (EJ 38(5): 451-456, 1991). The diagnosis was confirmed after the three therapeutic procedures (reduction of amount of each fluid intake, discontinuation of infant-feeding bottles, and substitution of water for juice and barley tea) were successfully taken within four months. The other five cases had been misdiagnosed as DI (EJ 38(5): 451-456, 1991). The diagnosis was confirmed after the three therapeutic procedures (reduction of amount of each fluid intake, discontinuation of infant-feeding bottles, and substitution of water for juice and barley tea) were successfully taken within four months. The other five cases had been misdiagnosed as DI (EJ 38(5): 451-456, 1991).

Conclusions: The plateau of urine osmolality in strict water restriction is pivotal in diagnosis of habitual polydipsia: Approaches of diagnosis in habitual polydipsia in infants.

**P2-d2-502 Others**

**Description of lifestyle habits of parents and children living in an underprivileged district in Toulouse (South of France)**

Béatrice Jourié1; Marie Dupuy1; Farida Ghrbi1; Catherine Payen1; Maryse Fouroux1; Agnès Lasbouygues2; Cécile Abbé1; Isabelle Renhas1; Mathis Tauber1

1Children Hospital, Endocrinology, Bone Diseases, Toulouse, France; 2City Hall of Toulouse, Social Center of Bellefontaine, Toulouse, France

Objective: Description of lifestyle of adults and children living in an underprivileged district.

Method: Recruitment in health and social centers of 200 adults willing to answer to a 30-min declarative questionnaire on lifestyle habits of their family. Questionnaires were conducted by volunteer medical students.

Results: - Population: - Age (median [P25-P75]): 36 [27-49] years - Sex ratio: 73.5% women - Origin country: 50% from North Africa - Working parents: 63% of men and 40% of women - Family incomes: low in 62.5% - Number of children/family (median [P25-P75]): 2 [0-3] - Age of children (median [P25-P75]): 9 [4.5-13] years - Overweight prevalence: - Adults: 55% of overweight (BMI≥25 kg/m) with 20.5% of obesity (BMI≥30 kg/m) - Children: 21.5% were obese using French reference curves - Lifestyle habits: - Diet: About 90% of children drink soft drinks and eat sweet products daily. All children don’t eat enough starchy food and half of them eat less than 3 fruits and vegetables per day. Parents believes: about 90% think that fruits and vegetables are good for health while 35% think that starchy food favor weight gain. - Physical activity: Half of the parents have a low level of physical activity. More than 2/3 of children practice regular physical activity. - TV watching: About 2/3 of the families watch TV during meals. 45% of children watch TV more than 2 hours/day during the week and 62% during the week-end.

Conclusions and Perspectives: These results show that children and their parents living in this underprivileged district have poor lifestyle habits. These data prompt us to implement in these same health and social centers educative programs involving the whole family.

**P2-d2-503 Perinatal Endocrinology**

**Estradiol in cord vein serum in girls - correlations to IGF-I, gestational age and size at birth**

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IGF-1 is a major growth factor during intrauterine life. It is well known to correlate to size at birth and placental size. Some studies have shown gender dimorphism in IGF-1 levels at birth, possibly due to different sex steroid patterns. It is not known to what extent estradiol influences fetal and placental growth and thereby size at birth. Earlier studies are few and inconclusive. The objective of the study was to study estradiol in cord vein serum from newborn girls and correlate it to IGF-1 levels, gestational age and size at birth. 49 girls were studied. They were recruited from a population based cohort of 247 newborns. Gestational age was mean (SD) 34.7 (1.2) weeks. Birth weight was 2430 (525) gram and birth length was 49.6 (2.4) cm. 14 girls were twins and 35 singletons. Cord venous blood was collected after birth. Serum estradiol concentrations were measured by a RIA (Spectria estradiol; Orion Diagnostica, Espoo, Finland). IGF-1 was measured by an IGFBP-blocked RIA (Mediagnost, Tübingen, Germany). Correlation analyses were made with Spearman non-parametric rank correlation. Estradiol levels in cord vein serum correlated to IGF-1 (r=0.42, p<0.01), gestational age (r=0.40, p<0.01), birth weight (r=0.32, p<0.05) and birth length (r=0.36, p<0.05). Interestingly, twins had lower estradiol levels 5870 (4860) pmol/L than singletons 16920 (12860) pmol/L, p<0.001 with Mann-Whitney U-test. IGF-1 levels did not differ between these groups. This study in newborn girls showed that size at birth correlated to cord estradiol levels, which interestingly also correlated to IGF-1 levels. Whether or not estradiol regulates intrauterine growth and the gender dimorphism in IGF-1 levels cannot be answered, but merits further investigations in a larger group of newborns of both genders.
Insulin sensitivity in prematurely born adults: Relation to preterm growth restraint (PGR)

**Objective:** The postnatal growth of children born preterm appropriate for gestational age is often retarded, leading to inappropriate weight or length at term age. This condition, called preterm growth restraint (PGR), is associated with diminished adult height. Preterms are at increased risk to develop insulin resistance, but the risk for the PGR subgroup is not known.

**Methods:** Childhood growth patterns and insulin sensitivity, measured by the hyperinsulinemic euglycemic clamp, were investigated in young adults. 17 preterm born subjects small for gestational age (SGA), 12 preterm born subjects appropriate for gestational age with postnatal growth retardation (AGA-PGR) were compared with 28 preterm born subjects appropriate for gestational age without postnatal growth retardation (AGA-nonPGR).

**Results:** Insulin sensitivity expressed as M-value (glucose disposal mg/kg/min) was lower in AGA-nonPGR (8.9) than in SGA (11.0) subjects, while a trend was observed in comparison to AGA-PGR subjects (10.4). These differences disappeared after adjustment for body size. Linear growth between 3 months and 21 years of age was different between AGA-nonPGR and SGA subjects (p=0.003). Linear growth was also different between AGA-nonPGR subjects and the combined AGA-PGR and SGA subjects (p=0.007). Changes in weight and BMI sds between 3 months and 21 years were not different between the groups.

<table>
<thead>
<tr>
<th>SGA vs. AGA-PGR</th>
<th>SGA vs. AGA-nonPGR</th>
<th>AGA-PGR vs. AGA-nonPGR</th>
<th>AGA-PGR vs. AGA-PGR</th>
<th>SGA vs. AGA-PGR</th>
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</thead>
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<tr>
<td>B (95% CI)</td>
<td>P</td>
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<td>P</td>
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<tr>
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<td>0.15</td>
<td>0.25</td>
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<tr>
<td>Weight sds 3 months</td>
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<td>0.06</td>
<td>0.25</td>
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<tr>
<td>Length sds 3 months</td>
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<td>0.06</td>
<td>0.36</td>
<td>0.03</td>
<td>-0.11</td>
</tr>
</tbody>
</table>

Regression analysis of insulin sensitivity expressed as logM-value. Crude; BWsds and BLsds: logM-value adjusted for birth weight sds and birth weight sds according to Niklasson; Weight and length at 3 months: logM-value adjusted for weight sds and length sds at 3 months according to Dutch references.

**Conclusion:** insulin sensitivity is lower in subjects born prematurely with SGA and PGR than in subjects born prematurely without PGR. These differences are related to birth weight and early postnatal growth.

Hyperinsulinism and insulin insensitivity precedes pregnancy induced hypertension

**Objective:** Pregnancy induced hypertension (PIH) affects 10% of pregnancies and is associated with an increased risk of subsequent cardiovascular disease. PIH may be associated with an increased incidence of the metabolic syndrome. Whether pregnancy simply serves to amplify tendencies towards higher blood pressure and the Metabolic Syndrome is unclear. We have compared fasting glucose, insulin and HOMA measures of insulin sensitivity and beta cell function at 12 weeks of gestation in 1650 Caucasian women (mean age 31.0 years) singleton pregnancies with the development of PIH or preeclampsia later in the pregnancy. Table 1 Weight, BMI, blood pressure and metabolic measures at 12 weeks gestation