The AGE-RAGE pathway has been considered as an important mediator of early glomerular changes in diabetic patients. Several growth factors and vasoactive molecules involved in early nephropathy have been shown to be directly produced as a consequence of RAGE activation. Furthermore, the C-truncated form of the endogenous secretory RAGE (esRAGE) has been shown to reveal the system function. Therefore, we tested whether impaired esRAGE concentrations are associated with early signs of diabetic nephropathy (DN), defined as changes in kidney volume and renal resistive indexes (RI). A group of 56 prepubertal and pubertal normoalbuminuric patients with type 1 diabetes (T1D) at least 4 years diabetes duration, were recruited and compared with 54 age, sex and pubertal stage matched controls. In all subjects, anthropometric measurements (height, BMI) were evaluated and esRAGE was measured in fasting blood samples. Kidney ultrasonography was performed and renal volume was calculated using the ellipsoid formula and adjusted for body surface. In addition, doppler ultrasonographic registration of intrarenal RI was performed. esRAGE was significantly lower in prepubertal (0.45±0.18 vs 0.9±0.8 ng/ml, p=0.013) and pubertal (0.4±0.17 vs 0.75±0.48 ng/ml, p=0.02) patients with T1D compared with controls. In both prepubertal and pubertal subjects, mean-kidney volume (p=0.03 and p=0.01) and mean doppler RI values (p=0.013 and p=0.002) were significantly increased in T1D patients when compared with controls. In a multiple regression analysis, an inverse relationship between esRAGE and adjusted kidney mean volume (p=0.042, beta=-0.367) was documented in diabetic patients. This study demonstrated decreased levels of esRAGE which appeared to be strongly related to increased kidney volume and RI in normoalbuminuric prepubertal children and adolescents with T1D, suggesting a potential role of esRAGE in the development of kidney disease. However, further longitudinal studies are required in order to define a causal-effect relationship between esRAGE and the risk of DN later in life.

**P2-d3-676 Pancreas 2**

**Decreased esRAGE levels are associated with increased kidney volume and renal resistive indexes in normoalbuminuric prepubertal children and adolescents with type 1 diabetes**

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According to the nerve conduction analysis of motor and sensory nerves in the pediatric patient with intermediate and long standing DM there was significant difference in nerve conductivity between diabetic and control groups. The fact that none of the diabetic patients had neurological complaints or clinical manifestations of nerve abnormalities proved that nerve damages appear much earlier than clinical symptoms. DPN is much more prevalent in diabetic patents than originally accepted. In our study we found that DPN can be found subclinically on early stages and should be addressed more on early stages. It also confirmed that NC-Stat system is non-invasive, sensitive tool for measurement of motor and sensory nerve conductions and detection DPN in children and adolescents.

**P2-d3-677 Pancreas 2**

**Subclinical diabetic peripheral neuropathy (DPN) is a frequent complication in children with diabetes as measured by of the NC-Stat® System**

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Subclinical DPN is common among children with type 1 diabetes (DM1). There is limited data available on screening of children with DM1 before they presented with clinical symptoms of DPN. Nerve conduction studies (NCS) are the most objective measure of DPN. Regular use of NCS in children with diabetes has been limited by lack of suitable technology. The NC-Stat® System is a nerve conduction testing system that uses prefabricated electrode assemblies and analyzing program software. All subjects were studied with a nerve conduction testing system. The instrument acquired and reported the mean Distal Motor Latency (DML), Distal Sensory Latency (DSL) and median F-wave parameters for nerves. Nerve conducting studies were performed on median nerve, peroneal nerve and bilateral sural nerves. Control group participants had been chosen randomly by medical history and Hba1C<6. Study group participants were children with DM1 for 4 or more years and normal neurological data. From nerve conduction analysis of all four nerves showed a significant difference between diabetic groups and control as follows: median nerve in F-wave mean, DML and DSL; peroneal nerve in F-wave mean and maximum F-wave; bilateral sural nerves in DSL and conduction velocity.
completed by adolescents and parents/carers attending 21 international centers. HbA1c (DCCT adjusted) measured centrally.

Results: Questionnaires were completed by 2062 adolescents (age 14.4 ± 2.3 yrs; 50.6% male; diabetes duration 6.1 ± 3.5 yrs). Mean HbA1c = 8.2% ± 1.4 with significant difference between centers (F = 12.3; p < 0.001) range 7.4 to 9.3%.

Significant correlation between parent (r = 0.20) and adolescent (r = 0.21) reports of their ideal HbA1c and actual results and stronger association between what parents (r = 0.39) and adolescents (r = 0.4) report as the HbA1c they would be happy with and actual result.

Significant differences between centers on both parent and adolescent reports of ideal HbA1c and the result they would be happy with (8.1 < F > 17.4; p < 0.001). Greater consistency between various members of a team within a center was associated with lower HbA1c. Adding these variables as co-variates substantially reduces the effect of center on HbA1c (center alone F = 3.27)

Conclusions: Clear and consistent setting of glycemic targets by diabetes teams is strongly associated with HbA1c outcome in adolescents. Target setting appears to play a significant role in explaining the differences in metabolic outcomes between centers.

P2-d3-679 Pancreas 2
Longitudinal risk factors for deterioration of insulin-resistance and development of glucose metabolism disorders in obese children and adolescents
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Childhood obesity and its complications are increasing worldwide. Little is known about the long-term outcome of Insulin resistance (IR), impaired glucose regulation (IGR) and T2DM in obese youth. We examined the development of IR, IGR/T2DM hypothesising that relative weight gain and transition of puberty are major risk factors for the deterioration of glucose metabolism. In the pediatric Obesity Centre 126 obese children and adolescents (12.96 ± 3.1 years, 62 boys, mean BMI-SDS 2.85, 38% immigrational background) with high risk for T2DM (ADA-criteria) underwent oral Glucose Tolerance Testing (oGTT) twice. Mean follow-up was 19.7 (± 10.6) months. Possible impact-factors on IR were tested by logistic analysis. 77.8% had IR at baseline, prevalence of MetS improved significantly (61% vs. 47.6%, p = 0.02). Out of 90 patients (R-HOMA >95th P), BMI-SDS did not change in the meantime, prevalence of IR-indices improved (R-HOMA > 0.2; ISI > 2.1; p = 0.001), increased IR (R-HOMA > 0.2; ISI > 2.1; p = 0.001) and 10% developed T2DM. Though more obese than those with NGR at baseline, relative weight of this group stayed stable (1st oGTT: 4.4% T2DM. At 2nd oGTT this subgroup showed weight gain (BMI-SDS 2.76 at 1st oGTT vs. 2.95 at 2nd oGTT; p = 0.001), increased IR (R-HOMA 4.54 at 1st oGTT; 5.4 at 2nd oGTT; p = 0.001) and 20% had onset of puberty. Of n=30 who initially showed IGR 33.3% did not change, 56.7% improved to NGR, and 10% developed T2DM. Though more obese than those with NGR at baseline, relative weight of this group stayed stable (1st oGTT: BMI-SDS 3.14; 2nd oGTT: BMI-SDS 3.17), IR-indices improved (R-HOMA 1st oGTT: 6.43; 2nd oGTT 4.5; p = 0.01, ISI 1.45 vs. 2.1; p = 0.001). None had BMI-SDS 3.14; 2nd oGTT: BMI-SDS 3.17), IR-indices improved (R-HOMA > 0.2; OR = 8.05, p = 0.012, compared to co-variates substantially reduces the effect of center on HbA1c (center alone F = 3.27)

Conclusions: Clear and consistent setting of glycemic targets by diabetes teams is strongly associated with HbA1c outcome in adolescents. Target setting appears to play a significant role in explaining the differences in metabolic outcomes between centers.

P2-d3-680 Pancreas 2
Continuous glucose monitoring system targets mean glycemia, decreasing the number of hyperglycemic episodes, promoting a better metabolic control on long term
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Objective: To compare efficacy of CGMS with SMBG (nine points testing) in improvement of glycemic control in pediatric type 1 diabetic patients.

Research Design and Methods: A total of 80 type 1 diabetic patients, 39 boys, and 41 girls, mean age 12.75 ± 3.67 years, with HbA1c > 8% and diabetes duration of 5.34 ± 3.50 yrs, were randomized into an experimental/CGMS and into the control/SMBG group. The CGMS group wore 72 hrs CGMS sensor (Medtronic MiniMed, Northridge, CA). Both groups were instructed to get 9 points SMBG testing during 3 days at the beginning, 3 and 6 months of trial, as well as corresponding HbA1c levels.

Results: There was a significant improvement in HbA1c at 3 and 6 months, in both, experimental (from 10.0 to 8.6%; p < 0.001) and the control (from 10.2 to 8.9%; p < 0.001) group, without significant difference in between two groups at 3 months (0.15 and 0.72) and after 6 months (0.12 and 0.7). Nevertheless there was a significant decrease in average number of hyperglycemia at 6 months (p = 0.009), and no increase in average number nor frequency of hypoglycemia (p = 0.11, and p = 0.25).

Conclusion: CGMS improves metabolic control as well as conventional SMBG. Yet CGMS provides a better insight in mean glycemia profile and therefore possibly promotes a persistant improvement in mean glycemia on a long run, with more time at target glycemia, and less time with nocturnal or any time hyperglycemia, hyperglycemia.

In Type 1 Diabetes Mellitus in children, many factors increase the risk of severe hypoglycemia. The real-time continuous glucose monitoring system (CGMS) helps patients achieve better glycemic control by allowing for earlier warning of erratic blood sugars and lessening the anxiety and fear of hypoglycemia. The objective of this study was to analyze the benefits of CGMS on glycemic control and to assess patients’ perceptions of the usefulness of the device. A total of 22 patients on insulin pump therapy were included in the study. Of the 22 patients, 14 used CGMS as a short trial period (4-6 weeks, ST) and 8 as long term tool (2 months to 18 months, LT). The age range was 4 to 22 years. 19 patients completed a questionnaire. Mean HbA1C in 22 patients before CGMS was 9.1% ± 1.9 and 4 to 8 weeks after on CGMS was 8.4% ± 1.8. The drop was statistically significant (paired t-test, p < 0.05). There was an improvement in the HbA1C in 90% of patients in ST. In 8 LT patients, average HbA1C before CGMS was 8.9% and 3 to 18 months after was 8.2%.

Based on the questionnaire, 95% preferred to continue the CGMS. Hypoglycemia prevention was the most common benefit appreciated (95%), followed by elimination of hypoglycemia-related anxiety (90 %), ease of pattern management (89%), improvement of diabetes control (84%), feeling of safety in school (84%), improvement of quality of life (84%) and ease of diabetes care (74%). Uncommon negative effects included irritation by the sensor alarm (37%), interference of daily routine by sensor alarm (26%), and skin irritation (26%). CGMS improves quality of life and glycemic control both in ST and LT use in children. The negative effects are uncommon and do not affect the decision to use CGMS.
Fasting plasma Ghrelin levels in well and poorly controlled type 1 diabetic children

**Aim:** In type 1 diabetic patients it was found that plasma ghrelin levels were elevated and with the prompt insulin therapy ghrelin levels returned to normal. It was also reported that low levels of ghrelin are negatively correlated with the degree of insulin resistance. There is a strong relationship between ghrelin levels and insulin metabolism. The aim of our study was to investigate ghrelin levels in well-controlled and poorly controlled type 1 diabetes mellitus children.

**Materials and Methods:** Twentyeight well controlled type 1 diabetic children, 18 poorly controlled type 1 diabetic children and 25 healthy controls were investigated. The mean age of well-controlled diabetics was 12.8±4.7 years (6.8-16.4 years), of poorly controlled diabetics was 13.4±4.1 (8.0-17.5 years) and of the healthy controls 12.1±3.6 years (7.5-16 years). For the last one year mean HbA1c levels in well controlled diabetics was 7.1%, in poorly controlled diabetics 9.2%. All children were analysed for the fasting plasma ghrelin levels at 08.30, in the morning.

**Results:** Plasma ghrelin levels were higher in poorly controlled group (324±145 fmol/ml) compared to well controlled diabetics (238±157 fmol/ml) and healthy controls (204±125 fmol/ml). Ghrelin levels were similar in well-controlled diabetes and healthy controls. There was no relationship between the body mass index, duration of insulin therapy and plasma ghrelin levels.

**Conclusion:** Negative correlation between HbA1c and plasma ghrelin levels in diabetes (p=0.05, r=0.305).

**Discussion:** Diagnosis of monogenic diabetes due to GCK mutations should be considered when fasting hyperglycemia is persistent and stable, hemoglobin A1c is just below or above the upper limit of normal range, in a OGTT the increment is small (typically <3.5 mmol/L) and one parent is affected. Testing glucokinase gene confirms the diagnosis.

Polygenic diabetes is rising worldwide, more remarkable in very young children. We evaluated clinical and autoimmune characteristics at the onset of DM1, in children diagnosed before 4 years of age, comparing them with those of subjects diagnosed later in childhood. We published 28 consecutive patients admitted to our clinic, from 1 January 2004 to 31 December 2007: 71 subjects (24.6%) were younger than 4 years (early onset:
Achieving optimal glycemic control in children with type 1 diabetes (T1D) is challenging. While the introduction of new insulin analogs has provided the potential for more physiologic basal/bolus insulin therapy, the large number of daily injections may contribute to compliance problems. As a compromise, we instituted a twice daily insulin regimen consisting of aspart or lispro mixed with NPH at breakfast and separate injections of aspart/lispro and detemir at dinner in newly-diagnosed patients. Carbohydrate counting was introduced at diagnosis and carbohydrate:insulin ratios and correction factors, particularly during the honeymoon period, were calculated. However, children demonstrated a high variety in HbA1c levels. We determined to what extent tracking of lipid levels occurred in children with DM1 and if it was correlated with glycemic control. Furthermore, we assessed the relationship between lipid levels and glycemic control, familial factors, BMI and diet. In 116 children with DM1 we determined retrospectively between 1996 and 2007 lipid- and HbA1c-levels, body mass index and duration of DM1. In a subgroup of 38 children diet and family history was assessed. As control group we used 17 children from our endocrine outpatient department and data from literature. Cholesterol and LDL-cholesterol concentrations remained strongly increased (> 5.2 mmol/l; >3.4 mmol/l) in respectively 50 and 83% of DM1 patients during the study. A high variety in HbA1c percentage was positively correlated with a high variety in cholesterol concentrations. Cholesterol concentrations were positively correlated with duration of DM1, age and HbA1c-percentage, but not with body mass index. Children with a positive family history for diabetes or heart attacks had higher cholesterol-, LDL-C- and lower HDL-C-levels. The diet of children with DM1 was similar to that of healthy children and showed no correlation with lipid concentrations. Tracking of lipid levels occurred in DM1 patients and was associated with glycemic control. Regular monitoring of lipid concentrations in children with type 1 diabetes and checking for associated cardiovascular risk factors is mandatory to identify high-risk patients. In DM1 patients at high-risk for atherosclerosis, optimization of glycemic control should be pursued and treatment with lipid-lowering medication should be considered.

In children with type 1 diabetes (DM1) poor glycemic control and abnormal lipid levels are related to macro- and micro vascular complications. In healthy children the chances to keep high lipid levels at adult age are 40-60%. Little is known about tracking of lipids in children with DM1 and about factors that influence their lipid levels. We determined to what extent tracking of lipid levels occurred in children with DM1 and if it was correlated with glycemic control. Furthermore we assessed the relationship between lipid levels and glycemic control, familial factors, BMI and diet. In 116 children with DM1 we determined retrospectively between 1996 and 2007 lipid- and HbA1c-levels, body mass index and duration of DM1. In a subgroup of 38 children diet and family history was assessed. As control group we used 17 children from our endocrine outpatient department and data from literature. Cholesterol and LDL-cholesterol concentrations remained strongly increased (> 5.2 mmol/l; >3.4 mmol/l) in respectively 50 and 83% of DM1 patients during the study. A high variety in HbA1c percentage was positively correlated with a high variety in cholesterol concentrations. Cholesterol concentrations were positively correlated with duration of DM1, age and HbA1c-percentage, but not with body mass index. Children with a positive family history for diabetes or heart attacks had higher cholesterol-, LDL-C- and lower HDL-C-levels. The diet of children with DM1 was similar to that of healthy children and showed no correlation with lipid concentrations. Tracking of lipid levels occurred in DM1 patients and was associated with glycemic control. Regular monitoring of lipid concentrations in children with type 1 diabetes and checking for associated cardiovascular risk factors is mandatory to identify high-risk patients. In DM1 patients at high-risk for atherosclerosis, optimization of glycemic control should be pursued and treatment with lipid-lowering medication should be considered.
Insulin glargine is a long-acting insulin analogue that is slowly absorbed after subcutaneous injection. After intramuscular injection severe hypoglycaemia has been reported (Diabetic Med 2005). We report the case of a boy who experienced hypoglycaemias after glargine injection. A 15-yr old boy (weight: 75 kg) with type 1 DM (onset: 2 7/12 yrs) switched at the age of 13 9/12 yrs from 2 injections of insulin Mixtard 30 to glargine (single dose of 21 U at 9:30 PM) and long-acting analog (i.e. GA and DE) administrations in fairly controlled T1DM children. Although slight difference in metabolic outcome was recorded than HRI use, PAI-based treatment presented higher therapy compliance and easy self management mainly depending to short-waiting action-start of PAs and longer-action duration than HRIs.

**Objective:** To compare clinical outcome of meal administration of premixed insulin analogs (PIAs; 50-70% short-acting with intermediate-acting insulin analogs) vs. human regular insulins (HRIs) in pediatric (group 1) aged 6.0-10.0 yrs and adolescent (group 2) aged 11.0-17.9 yrs subjects with type 1 diabetes (T1DM) basally treated with either insulin glargine (GA) or detemir (DE).

**Methods:** We tested a new "basal-mix" insulin scheme based on meal PAI and long-acting analog (i.e. GA and DE) administrations in fairly controlled T1DM children. Although slight difference in metabolic outcome was recorded than HRI use, PAI-based treatment presented higher therapy compliance and easy self management mainly depending to short-waiting action-start of PAs and longer-action duration than HRIs.

**Results:** No patients avoided meal PAI treatment, and no severe hypoglycaemia or other adverse effect was recorded. During GA and DE treatments, slightly but significantly (P=0.05; vs. previous HRI use) HbA1C% decrease was detected both in group 1 and 2 during PAI-based treatments (total 0.35±0.05 U/kg/day). No significant difference was detected between GA and DE treatments. Interestingly, meal PAI use significantly (P=0.05) improved pre-prandial glycemic mean and therapy compliance in both groups 1 and 2 either GA- and DE-treated. Furthermore, parent management was improved (P=0.05) by PAI use in group 1 especially during vomiting illness (P=0.01).

**Conclusion:** Meal use of premixed insulin analogs vs. human regular insulins improves life quality in healthy T1DM basally treated with insulin glargine or detemir.

**P2-d3-699 Pancreas 2**

**Severe early hypoglycaemia after subcutaneous injection of insulin glargine**

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Glutamic acid decarboxylase (GAD) is a rate-limiting enzyme that catalyses the conversion of glutamic acid into γ-aminobutyric acid, a major inhibitory neurotransmitter of the central and peripheral nervous system. Glutamic acid decarboxylase can be detected in GABAergic neurons and in pancreatic β-cells, testis, ovary, liver, kidney and adrenal gland. GAD65 isoform is one of the major antigens in type 1 diabetes mellitus (T1DM). Immune response to islet cell autoantigens plays a pivotal role in the autoimmune process which lead to clinical onset of type 1 diabetes mellitus. Moreover, anti-GAD antibodies are found in neurological disorders like Stiff-man syndrome, cerebellar ataxia and epilepsy. We describe a young patient with type 1 diabetes mellitus who developed a complex and severe epileptic phenotype. When 3.5 years old, he presented epilepsy partialis continua, associated with focal lesion on magnetic resonance imaging and anti-GAD antibodies in his cerebrospinal fluid. This condition was followed by drug-resistant temporal lobe epilepsy.
that was subsequently complicated by continuous spike-waves during slow sleep (CSWS), despite neuroimaging normalization and disappearance of anti-GAD antibodies in cerebrospinal fluid. CSWS is a specific age-related epileptic encephalopathy of childhood, characterized by almost continuous (>85%) bilateral and diffuse slow spike-waves during slow-wave sleep and associated with behavioural and neuropsychological impairment. Immunosuppressive treatment with corticosteroids led to a significant electro-clinical response. To our knowledge, this is the first description of a severe and complex epileptic phenotype with evolution to epileptic encephalopathy in a case of T1DM in which CSF analysis, neuroradiological findings and response to immunosuppressive therapy suggest a pathogenic role of anti-GAD antibodies.

**P2-d3-693 Pancreas 2**

**Reduced aromatization due to loss of subcutaneous fat?**

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Familial partial lipodystrophy type Dunnigan (OMIM #151660), an autosomal dominant disorder is caused by mutations in the lamin A/C gene (LMNA) localised on chromosome 1q 21-22. It encodes nuclear lamina proteins and causes a spectrum of diseases affecting muscle, nervous system or adipose tissue. Prevalence is described about 1:15 millions. Beginning in puberty after a normal childhood, FPLD is characterized by extreme loss of subcutaneous fat from the extremities and trunk, but increased visceral fat. In contrast, accumulation of fat occurs in the head and neck region resembling cushing’s phenotype. FPLD proceeds to diabetes and cardiovascular complications due to insulin resistance. Retinol binding protein 4 (RBP4) is a newly discovered adipokine, elevated in insulin resistance and obesity. Correlation of RBP4 with fat mass has been described. We observe a family over 3 generations with genetically proven FLDP (lamin A/C-Gen-Mutation G-->T with R482L). Parameter of insulin resistance and lipids were normal during childhood and started to be pathological during adolescence. After puberty elevation of androstendion, triglycerides, cholesterol, insulin and plasma glucose were measured (table). In contrast to the known physiological correlation we found in FLPD with decreasing fat mass increased RBP4 levels at 5/ 20/ 44years: 20,4/ 66,7/ 82,2 (normal: 30-60µg/l). Other adipocytokines (tumour necrosis factor-alpha, resistin, leptin and adiponectin) were normal. We conclude, in patients with FPLD and regular liver function, androstendion (tumour necrosis factor-alpha, resistin, leptin and adiponectin) were normal.

**P2-d3-695 Pancreas 2**

**Prevalence of mood and posttraumatic stress disorders among mothers of diabetic children and their impact on their children’s glycemic control**

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Psychological dysfunction in parents of diabetic children may influence their children’s glycemic control. The aim of this study was to examine the presence of depression, anxiety and Posttraumatic Stress Disorder (PTSD) among mothers of diabetic children and their possible impact on their children’s glycemic control. We assessed 88 mothers of children with Type 1 diabetes mellitus (28 newly diagnosed and 60 of long-standing diabetes), aged 38±6.8 years, using the 17-item PTDS scale, the Beck Depression Inventory (BDI), the Spielberger’s modified Greek state-trait anxiety inventory and a Major Life Events Questionnaire. All 88 children (39 boys), aged 10.9±4.2 years, were regularly followed at the Diabetes Center of the First Department of Pediatrics of Athens University. The association of maternal PTSD, anxiety, depression and major life events with demographic data, diabetes duration and glycemic control was investigated. A significant positive correlation was found between maternal PTSD score at baseline and HbA1c levels in newly diagnosed children (r=0.45, p=0.039). Greater score on anxiety scale was found in mothers whose children were recently diagnosed (53.6±13.1 vs. 47.3±13.8, p=0.045). Also, greater scores on the BDI scale were found among married mothers than single/divorced/windowed ones. A significant negative correlation was observed between PTSD and mother’s age, indicating that younger mothers had less coping abilities (r=-0.23, p=0.032). Additionally, all scales were significantly inter-correlated with correlation coefficients ranging from 0.53 to 0.67 (p<0.001). In long-standing diabetes, greater scores for state (49.4±14.2 vs. 41.8±11.1, p=0.037), trait (43.6±10.3 vs. 37.8±7.4, p=0.046), BDI (10.9±9.9 vs. 7.0±4.9, p=0.048) and PTSD (13±3.2 vs. 8.0±7.6, p=0.049) of the mothers were associated with worse glycemic control. In conclusion, depression, anxiety and PTSD of the mothers have a negative impact on their children’s glycemic control, suggesting that mothers of diabetic children need psychological evaluation, follow-up and support.

**P2-d3-694 Pancreas 2**

**Glucose metabolism is significantly impaired in non-diabetic CF patients during acute exacerbation**

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Background: The development of diabetes in patients with CF has been associated with a decline in their overall clinical and pulmonary function. Patients with CF and normoglycemia (CF-NG) have higher but still normal glucose levels in Oral Glucose Tolerance Test (OGTT).

**Objectives:** To analyze the glucose metabolism and its association with pulmonary function in CF-NG patients specifically during exacerbations

**Methods:** CF-NG patients underwent OGTT and intravenous glucose toler-

tance test (IVGTT) during exacerbation and 3-4 weeks after complete resolution.

**Results:** Of the 10 recruited patients 2 were found diabetic by OGTT and were excluded. All 8 remaining patients displayed diabetic glucose tolerance with glucose levels of 233±8 and 262±11mg/dl at 90 and 120 min during exacer-

bation compared with normal levels of 154±21, 126±20mg/dl (p=0.002) measured during remission. IVGTT exemplified higher insulin release during exacerbation compared to remission (min 3; 305±80 vs. 216±40). When stu-

dying the ratio between glucose levels during exacerbation (using the area under the curve {AUC} of OGTT) and insulin secretion capacity (using AUC of 1+3 min insulin in IVGTT) a significant negative correlation was found (r=-0.64, p=0.09). Furthermore, we observed a negative correlation between FEV1 during remission and glucose levels at 2 hours after OGTT during ex-

acerbation (r=-0.88, p=0.002).

**Conclusion:** During exacerbation Non-diabetic patients exhibit early glucose intolerance. A higher release of first phase insulin suggests insulin resistance, but the failure to normalize glucose in the OGTT implies also an insulin se-

cretion defect. These findings may advocate studying the benefit of insulin administration during acute exacerbations in non-diabetic patients.
Heterozygous mutations of the KCNJ11 gene encoding the Kir.6.2 subunit of the K-ATP channel is a rarer cause of transient neonatal diabetes mellitus compared to anomalies of the imprinted region on chromosome 6q24. For about ~50% of all cases their diabetes will relapse in later life. We report a case of neonatal diabetes presented at the age of 50 days with remission at 8 months of age related with the R50Q mutation in the KCNJ11 (Kir.6.2) gene. The same defect has been found in his non diabetic mother and his recently diagnosed with “type2” diabetes maternal grandmother. Neurological features presented during DKA resuscitation are unlikely to be related with this specific genetic defect although cannot be excluded. This baby was born after an uneventful 37 weeks pregnancy from healthy non related parents with a birth weight of 2610 gr (+1.0 SD). Pancreatic autoimmunity (GAD, IAA Abs) has been negative since diagnosis and c-peptide was undetectable. Insulin needs dropped gradually from the initial 0.6 IU/kg/day dose until adequate glycemic control was achieved off insulin. The molecular proximity of the R50Q mutation with the ATP binding site residue within the Kir.6.2 molecule may affect the sensitivity of the K-ATP channel to increased ATP and reduced ADP concentrations and allow insulin secretion. The mechanism by which K-ATP channel result in a remitting/relapsing diabetes phenotype is not known. A Polish and Japanese individual with the same genetic defect have been described with similar phenotypic features apart from neurology.

**P2-d3-697** Pancreas 2  
**Risk factors associated with impaired glycaemic metabolism in cystic fibrosis**  
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**P2-d3-698** Pancreas 2  
**The effect of type one diabetes in pubertal growth**  
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Data regarding the influence of insulin dependent diabetes in pubertal growth has been scarce. Our purpose was to evaluate the influence of the disease and the effect of glycemic control on growth velocity in adolescents with insulin dependent diabetes mellitus. Retrospective review of one hundred patient files, fifty six males, was conducted. The duration of the disease was at least one year. Data regarding height velocity, medium annual glycated hemoglobin (HbA1c) and insulin requirements through eleven to fifteen years of age were retrieved (n=29 at eleven, n=36 at twelve, n=49 at thirteen, n=39 at fourteen and n=33 at fifteen years of age). Tanner-Whitehouse tables for height velocity were used as control population (fifth percentile). The Wilcoxon test was used to compare the median values and Spearman’s correlation coefficients were computed. P values < 0.05 were regarded as statistically significant. In our patients peak height velocity was inferior than control sample for both genders with statistical significance (males at thirteen (p=0.035) and fourteen (p=0.000) years of age and females at eleven (p=0.023), twelve (p=0.004) and thirteen (p=0.039)). We found that metabolic control evaluated by HbA1c was only significant for continuous growth after pubertal growth peak in males (p=0.02). There was no correlation between duration of the disease and statural growth in all age groups and in both genders (p>0.05). Authors concluded that peak statural growth is negatively influenced by type one diabetes, regardless of metabolic control. Glycemic control evaluated by HbA1c was important only in post pubertal growth in males in our sample. The duration of the disease has no significance in statural height in pubertal growth peak.

**P2-d3-699** Pancreas 2  
**Association of QT and QTc intervals in children and adolescents with diabetes mellitus type 1 with basic characteristics of the patients and the disease**  
A left atrioventricular block and severe hypokalemia were present. The record contained 40 electrodes and was collected between 1990 and 2000. The disease was stable and its treatment was not changed during the study. Data were collected retrospectively. The disease was stable and its mean±SD duration was 4.41±2.91 years. QT was measured on the resting 12 lead electrocardiograph and Bazett’s formula was applied for the calculations of QTc. Differences between sexes were evaluated by comparing means with t-test. The possible influence of age, BMI, diabetes duration, age at onset, type of treatment and glycosylated hemoglobin (HbA1c) was examined by using bivariate correlation analysis. Mean±SD QT was 361.44±30.06ms and mean±SD QTc was 354.48±29.22ms respectively, p=0.101. There was a positive correlation between QT and age (r=0.545, p=0.000), age at onset (r=0.309, p=0.015), and no association of QT with BMI, HbA1c, duration of therapy, type of treatment. QTc did not correlate with anyone of the above mentioned parameters. In conclusion, in diabetic children age and age at onset of the disease may play a significant role in the length of QT. Females exhibit longer QTc than males. Keywords: Diabetes Mellitus type 1, heart, electrocardiographic abnormalities, QT interval.
**P2-d3-700 Pancreas 2**

**Continuous blood glucose monitoring and insulin pump therapy using rapid acting insulin in a neonate with congenital adrenal hyperplasia (CAH) and neonatal diabetes mellitus (NDM)**

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1University Essen, Pediatrics, Essen, Germany; 2University Essen, Human Genetics, Essen, Germany

Background: Transient (TNDM) and permanent (PNDM) neonatal diabetes mellitus are rare conditions occurring in one of 400000-500000 live birth. TNDM occurs mainly with abnormalities on the long arm of chromosome 6 and methylation defects, whereas PNDM is characterized by defects in the genes for KCNJ11, ABCC8 or glucokinase. Congenital adrenal hyperplasia (CAH) is also rare occurring in one of 10000 live births in Western Europe, and is due to mutations of the CYP21 gene on chromosome 6.

Case Report: We report about a 3-day-old boy with vomiting and hypotremia (129 mmol/L). An elevated 17-OH-progesterone (>250 nmol/L, normal: <60 nmol/ml) was found on newborn screening and the salt wasting form of 21-hydroxylase deficiency was diagnosed. Treatment with fludrocortisone and hydrocortisone was initiated. Five days after start of treatment he developed hyperglycemia. Continuous measurement of blood glucose (CGMS, Medtronic Corp.) showed elevated levels, especially after meals and hydrocortisone intake. We started insulin pump therapy (ANIMAS, Med, Trust Corp.) using a rapid acting insulin. Insulin basal rate was increased (0.45 IE/kg/24 hours) over that recommended in neonates with NDM alone. The molecular analysis of the CYP21 gene revealed a homozygote mutation in the intron 2 splice site (656A>C/G; 656A>C-G). Mutations in the KCNJ11 and glucokinase genes in or in chromosome 6 were not found.

Conclusion: Hyperglycemia in neonates with CAH under treatment with hydrocortisone is rare. Neonatal diabetes mellitus should be considered in the differential diagnosis of this condition. Treatment with an insulin pump using rapid acting insulin resulted in a better control of blood glucose peaks after meals and hydrocortisone intake. Our data show that continuous glucose monitoring can identify high peaks of blood glucose caused by synergistic action of carbohydrate and glucocorticoid intake. In our patient with CAH and neonatal diabetes a higher dose of insulin was needed for a good metabolic control.

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**P2-d3-701 Pancreas 2**

**Diabetes mellitus in family members of obese pubertal children**

Mirjana Kovova; Simona Spasevska; Elena Sukarova-Angelovska; Nadezda Spasikova; Sinemis Hacisalihi; Elena Sukarova-Angelovska

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Obese children are at risk for developing diabetes mellitus (DM) later in life. DM in family members is considered an additional risk. The aim of our study was to assess the incidence of diabetes mellitus (DM) in family members of obese children and assess the association with metabolic parameters: BMI, HOMA index, and peak glycaemia and peak insulinemia on OGTT. Seventy-eight obese pubertal children were analyzed. Obesity was assessed by BMI calculation using CDC charts. Standard OGTT test was performed. Peak insulinemia and glycaemia were recorded. History of documented DM in immediate members of the patient’s family was recorded. Group with DM in family members was compared with group whose relatives did not have DM. Fifty one (65.4%) of children had a relative (one or more) with DM. DM appeared most commonly in grand mothers (35%). In 45 families, besides DM there were other risk factors such as hypertension, infarct or cerebral insult. Average BMI was 28.3±3.1 kg/m² vs 29.2±1.8 kg/m² with no significant difference. Peak insulinemia was 109±16.2 uIU/mL and 129.2±12.3 uIU/mL. HOMA index was 4.79±2.86 vs 4.68±3.27 respectively. Peak glycaemia did not differ between the two groups of patients, 7.28±3.1 mmol/L vs 7.89±1.2 mmol/L. Eleven children (5 boys and 6 girls) had normal insulin tolerance. All of them had a relative with diabetes mellitus. No correlation of the HOMA index or peak insulinemia and glycaemia with the presence of DM in the family was found. In conclusion, DM in family members appears as a common risk factor for obese children. Our analysis shows no correlation between the degree of obesity or insulin resistance with appearance of DM in families. Thus, all obese children should be treated as being at risk for developing DM.

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**P2-d3-702 Pancreas 2**

**Plasma C-reactive protein levels in children with newly diagnosed type 1 diabetes (T1DM) and ketoacidosis (DKA) and its correlation with systemic inflammatory response syndrome (SIRS)**

K Karayanni1; S Georga1; A Kardamis1; G Moulopoulos1; M Tsouvalas2; I Konstantopoulos1; A Vogiatzi1; I Papassotiriou1; C Karayanni1

1University of Athens, Diabetic Clinic, B Pediatric Department, Athens, Greece; 2Aghia Sophia Children’s Hospital, Department of Clinical Biochemistry, Athens, Greece; 3Penteli Children’s Hospital, Clinical Biochemistry Laboratory, Athens, Greece; 4Clinical Biochemistry Laboratory, Penteli Children’s Hospital, Athens, Greece

Background: Both elevated high sensitivity CRP (hsCRP) levels and pro-inflammatory cytokines have been reported as sensitive markers of systemic inflammatory response syndrome (SIRS) in adult patients with severe DKA, without infection.

Aims: Our aim was to assess the hsCRP changes during DKA in T1DM children and to study its usefulness as a marker of SIRS.

Patients and Methods: Our study included 19 children with newly diagnosed T1DM and DKA, without clinical symptoms of infection. WBC, hsCRP and IL-1β, IL-2, IL-6, IL-8, IL-10 and TNF-α cytokine levels were estimated prior to and at 6, 24 and 120 hours after treatment.

Results: We divided the patients into two groups: a) with severe or moderate DKA: PH<7.20, b) with mild DKA: PH<7.20. In group a the hsCRP levels were increased at 0th and at 6th and were significantly reduced at 24 hours after treatment of DKA (4.6 vs 4.0 mg/l, p=0.012). Also in group a, IL-6 levels, WBC and ANC were significantly increased at diagnosis and were reduced at 120hours (IL-6: 28.3 vs 11.8 pg/ml, p=0.003, ANC: 33.1x103 vs 3.1x103, p=0.003, WBC: 18.3x103 vs 6.7x103, p=0.003) without antibiotic administration. Inversely in group b, the hsCRP, IL-6, WBC and ANC were normal during the whole study period. Also in group a, hsCRP was positively correlated: prior to treatment with IL-6 (p=0.028), IL-8 (p=0.05), ANC (p=0.010) and WBC (p=0.023); at 24hours with IL-6 (p=0.002), IL-1β (p=0.05), IL-8 (p=0.014) and at 120hours with IL-10 (p=0.027), ANC (p=0.039), while no significant correlations were observed in group b.

Conclusion: Our results suggest that during severe or moderate DKA, hsCRP, IL-6, WBC and ANC levels are increased without the presence of infection. As DKA may be associated with a non-infectious form of SIRS, the presence of increased levels of hsCRP may serve as a useful marker of the risk of severe complications of DKA, especially of cerebral edema.

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**P2-d3-703 Pancreas 2**

**Thyroid function and thyroid autoimmunity in Turkish children with newly diagnosed type 1 diabetes**

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Type 1 diabetes (DM1) is frequently associated with autoimmune thyroid disease. Euthyroid sick syndrome (ESS) is an alteration of thyroid hormone values in the absence of a thyroid disease, which is seen in patients suffering from serious diseases such as diabetic ketoacidosis (DKA). Our aims were to evaluate the prevalences of thyroid-related antibodies and euthyroid sick syndrome (ESS), and to compare thyroid function of DKA group with non-DKA group. Thyroid hormones (free triiodothyronine; FT3, free thyroxine; FT4, total T3; TT3, total T4; TT4), thyrotropine (TSH), and thyroid-related antibodies (antibodies against thyroglobulin; anti-Tg and peroxidase; TPO-Abs) were studied in 175 children and adolescents (93 girls, 82 boys) with newly diagnosed DM1. Measurements were performed within two days of the initial diagnosis of DM1 and follow-up tests were performed the day 15th (except thyroid-related antibodies) and after one year. We classified the patients according to the presence (DKA group, n: 87) or absence (non-DKA group, n: 88) of DKA at initial diagnosis. The mean age of diagnosis was 8.6 years. Among 175 patients with DM1, 30 (17.1%) were positive for anti-TPO and/or antiTg. Eight of the 30 thyroid autoantibodies-positive patients suffered from
subclinical hypothyroidism and one had clinical hypothyroidism. Positivity of thyroid autoantibodies was more common in girls (67%) than in boys (33%). Fifty-four (30.9%) of the 175 patients had alterations of the thyroid hormones in accordance with ESS. There was significantly difference in HbA1c levels between patients with and without ESS. Among 54 patients with ESS, 40 (74%) were in DKA-group (p<0.05). Our study confirms the association between ESS and DKA. The frequency of positive thyroid autoantibodies was not higher in patients with DM than in healthy children in our region, thus we do not recommend screening thyroid autoantibodies at diagnosis in patients with DM1. Instead, TSH determination could be recommended to detect subclinical hypothyroidism.

P2-d3-706 Pancreas 2
Structure of pediatric diabetes in Latvia
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Children’s University Hospital, Children’s Endocrinology Centre, Riga, Latvia

Introduction: In 1993 the Latvian childhood diabetes register was established. All newly diagnosed diabetic patients <18 years have enrolled since 1993.

Aim: To describe the Diabetes incidence during the first 13 years.

Methodology: Data from Diabetes register and Latvian Statistics Agency.

Results: A total of 673 children with T1D < 18 years were diagnosed 1993 - 2006. There were 392 boys and 281 girls.

The mean incidence in each year per 100,000 was 2.74% (CI 0.8 - 4.1%). Analysis of the increasing incidence of T1D showed no escape from linearity, thus period and cohort effect could not be separated.

A total 18 children with T2D < 18 years were diagnosed 2002 - 2006, there were 12 girls and 6 boys. The age of the patients at the moment of diagnosis ranges from 9.5 years to 17 years. 17 of 18 patients have BMI to sex and age above 95th percentile. One case of T2D - patient with Prader - Willi syndrome.

2 patients diagnosed PNDM with clinical manifestation before 6 months of age and with detected heterozygous mutation R90C INS gene exon 3.

We have a family with two children with TNDM, who have not typical chromosome 6 abnormalities. The family will be tested for chromosome 15 mutations.

We suspect DIADMOAD’s by one girl with atrophy of the optic nerve, deafness and diabetes mellitus, but the genetic tests are not done.

In our register we have 6 patients with MODY and 1 patient with “double” diabetes. Total number of newly diagnosed all types of diabetes <18 years in register are 701 since 1993.

Conclusions: There is a continuous increase of T1D in Latvia; Incidence of T2D is increasing in Latvia, but is still much lower we expected; The main risk factors of T2D in our patients are: Overweight - 91%, overweight in the family - 55%, diabetes in the family - 72%; We suspect, that not all children with T2D are diagnosed, and further screening programs need to be work out; it is not easy to determine the type of diabetes - T1, T2, MODY or maybe “double” Diabetes, what is a really challenge for doctors to choose the best treatment.
Results:

<table>
<thead>
<tr>
<th></th>
<th>Girls</th>
<th>Boys</th>
<th>All Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMISDS diag.</td>
<td>-1.64 (1.02)*</td>
<td>-0.02 (1.17)</td>
<td>-0.67 (1.36)*</td>
<td></td>
</tr>
<tr>
<td>BMISDS 6 weeks</td>
<td>-0.81 (0.97)*</td>
<td>0.54 (1.0)</td>
<td>0.02 (1.18)</td>
<td>0.16 (1.18)</td>
</tr>
<tr>
<td>BMISDS 1 year</td>
<td>-0.58 (0.90)*</td>
<td>0.65 (0.98)</td>
<td>0.16 (1.11)</td>
<td>-0.16 (1.34)</td>
</tr>
<tr>
<td>waist/hip ratio</td>
<td>0.92 (0.05)</td>
<td>0.93 (0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBA1c(%)</td>
<td>8.8 (1.2)*</td>
<td>7.8 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (u/kg/day)</td>
<td>1.00 (0.31)*</td>
<td>0.82 (0.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T.cholesterol (mmol/l)</td>
<td>4.3 (0.45)*</td>
<td>3.79 (0.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>2.61 (0.53)*</td>
<td>2.02 (0.37)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean (SD), *p<0.05 boys vs girls, +p=0.05 patients vs controls

Conclusion: Normal body composition is restored 6 weeks after diagnosis and maintained at one year. Distribution of body fat (waist/hip ratio) is also normal at 1 year. Girls are thinner than boys both at diagnosis and thereafter, in contrast with published findings. Despite their similar age and stage of puberty and larger insulin dose, girls have a higher HbA1c at 1 year in keeping with a known increased risk of insulin resistance and DKA compared to boys. Girls also have a higher total cholesterol and LDL cholesterol (non-fasted). However, the implication of this is uncertain as the HDL and total cholesterol/HDL ratio is the same as the boys.

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**P2-d3-708 Pancreas 2**

**Glucokinase gene mutations in MODY 2 patients from south Italy**

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Background: Maturity onset diabetes of the young type 2 (MODY2) is a genetic form of diabetes mellitus caused by mutations in the glucokinase gene (GCK).

Methods: We screened the GCK gene by direct sequencing in 30 pediatric patients from South Italy, screened by a clinical and laboratory pattern suggesting MODY2 diagnosis. The mutation-induced structural alterations in the protein were analyzed by molecular modeling. The patients’ anamnestic, clinical and biochemical data were obtained.

Results: Mutations were detected in 16/30 patients (53%); 9/12 new mutations were identified (p.Glu70Asp, p.Phe123Leu, p.Asp132Asn, p.His137Asp, p.Gly162Asp, p.Thr168Ala, p.Arg392Ser, p.Glu290X, p.Gln106,Met107del). These mutations were found in the molecular regions involved in structural rearrangements required for catalysis. The prevalence of mutation sites was higher in the small domain (7/12: 59%) than in the large (4/12: 33%) domain or in the connection (1/12: 8%) region of the protein. Mild clinical and biochemical phenotypes were detected in all patients [mean (SD) fasting glucose 7.8 mMol/L (1.8)] and mean triglyceride levels were lower in mutated vs non-mutated GCK patients (p=0.04). A partial genotype-phenotype correlation was found in related patients (3 pairs of siblings) but not in two unrelated children bearing the same mutation.

Conclusion: The prevalence of MODY2 is high in clinically suspected children in southern Italy, and the GCK small domain is a hot spot for MODY patients from south Italy. At present it is not clear if the type of GCK mutation and the genetic background may play a relevant role in the MODY2 clinical phenotype.

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**P2-d3-710 Pancreas 2**

**Clinical-epidemiological parameters of type 1 diabetes mellitus by the national register data in children mellitus in Uzbekistan**

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Aim: to study region dependent epidemiological peculiarities of type 1 diabetes mellitus in children and adolescents by the National Register data within the period from 2000 to 2006.

Materials and Methods: epidemiological data was studied on the basis of re-ports and registration cards from 13 regional endocrinological dispensaries and the one in Tashkent. The registration cards included demographic and biochemical pa-rameters, the disease duration, type of insulin therapy, compensation degree, presence of late vascular complications and mortality causes.

Results: within the period from 2000 to 2006 type 1 diabetes mellitus prevalence in children increased from 7.5 to 10.2 per 100,000 of pediatric population. There was insignificant reduction of the prevalence from 28.3 to 21.2 per 100,000 of adolescent population mainly due to the registry registrati-on. The highest prevalence was observed in Tashkent-city (19.0 and 48.9 in chil-dren and adolescents) and in Tashkent region (13.9 and 38, respectively), the lowest one in the Republic of Karakalpakstan (5.7 in children) and in Kashkardarya region (3.3 in adolescents). As compared with 2000 the disease incidence in 2006 in children reduced from 2.7 to 2.1 per 100, 000 of pediatric population, the one in adolescents decreasing from 7.1 to 2.6 per 100, 000 of adolescent population. High incidence was observed in Tashkent-city (5.2) and in Navoi region (3.5). The highest incidence among ado-lescents was registered in Tashkent-city (5.5) and Tashkent- region (9.0). For the period of National Register the mortality rate reduced from 0.1 to 0.04 per 100, 000 of pediatric population, the data in adolescent one appearing during the time of register. In 2003 mortality in adolescents was 0.4 reducing to 0.25 per 100, 000 adolescent population due to improvement in quality of insulin therapy prescribe- tion.

Conclusion: progressive growth in type I diabetes mellitus among children and adolescents within the National Register period from 2000 to 2006 against reduction in incidence and mortality was observed.
Epidemiology of type 1 diabetes among children under 15 years of age in Navarre (northern Spain) between 1996-2007

Sara Berrade; Maria J Chueca; Alberto Sola; Goterí Echarte; Margarita Aliaga; Mirentxu Oyarzabal
Virgen del Camino Hospital, Pediatric Endocrinology, Pamplona, Spain

A retrospective and updated study of children under 15 years of age, diagnosed with TIDM in Navarre between January 1996 and December 2007. Besides, we evaluated the diagnostic orientation prior to onset of the disease at the different health care levels in children. Capture-recapture methodology has been applied, using as primary source the only reference tertiary hospital in Navarre, and as secondary source the data from other hospitals (private, limiting communities and adult endocrinology), primary care centers and the Diabetes Association of Navarre (CI >95%). Statistical analysis: SPSS. 170 children and adolescents (102 M 68 F) with a mean age of 9.1 years (range: 14 months-14.99 years) initially manifested the disease, with no significant seasonal variation. Annual mean: 14 cases. By time periods, the mean incidence among subjects under 15 years of age was 13.9 / 100,000 in 1996-2000, 20.6 / 100,000 in 2001-2005 and 21.8 / 100,000 in 2006-2007. On analyzing the tendency since 1975 (comparing the current incidence with that of a previous study conducted in the same geographical setting between 1975-1991) a clear increase in incidence is observed (Spearman correlation r=0.89), even in the 0-4 years age group (p=0.28). Regarding the place of diagnosis, 66% of the cases were diagnosed in primary care, 24% in hospital emergency services, 5.1% at home, and 3.2% in the pharmacy. A total of 26.5% had made medical consultations prior to the diagnosis, without suspecting the disease. The setting in which the diagnosis is made has not changed over the years (p>0.05). The incidence of TIDM in the pediatric population has clearly increased in recent years in Navarre. Orientation and diagnosis in the primary care setting have not improved over the years. Campaigns are thus needed to enhance awareness of the disease in different circles (primary care physicians and schools).

Characteristics of type 1 diabetes onset in children with diabetic ketoacidosis (DKA) in Navarre (northern Spain)

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The onset of type 1 diabetes mellitus (TIDM) in diabetic ketoacidosis (DKA) is a life-threatening situation that represents the main cause of morbidity and mortality in pediatric patients with TIDM. The objectives were to evaluate the frequency of DKA at diagnosis of TIDM among children under 15 years of age in Navarre (northern Spain); Population January 2007: 605,876 inhabitants; < 15 years of age: 88,055 (14.5%) and to analyze the characteristics of DKA (ISPAD Guideline) by age groups, time periods and place of diagnosis (primary care, emergency service, home or pharmacy). A retrospective and updated study of children and adolescents initially manifesting with DKA in Navarre between January 1, 1996 and December 31, 2007. Sample: 170 children and adolescents (102 males and 68 females) with a mean age of 9.1 years (range: 14 months-14.99 years) initially manifested the disease, with no significant seasonal variation. Annual mean: 14 cases. By time periods, the mean incidence among subjects under 15 years of age was 13.9 / 100,000 in 1996-2000, 20.6 / 100,000 in 2001-2005 and 21.8 / 100,000 in 2006-2007. On analyzing the tendency since 1975 (comparing the current incidence with that of a previous study conducted in the same geographical setting between 1975-1991) a clear increase in incidence is observed (Spearman correlation r=0.89), even in the 0-4 years age group (p=0.28). Regarding the place of diagnosis, 66% of the cases were diagnosed in primary care, 24% in hospital emergency services, 5.1% at home, and 3.2% in the pharmacy. A total of 26.5% had made medical consultations prior to the diagnosis, without suspecting the disease. The setting in which the diagnosis is made has not changed over the years (p>0.05). The incidence of TIDM in the pediatric population has clearly increased in recent years in Navarre. Orientation and diagnosis in the primary care setting have not improved over the years. Campaigns are thus needed to enhance awareness of the disease in different circles (primary care physicians and schools).

Diabetes management in a tertiary center - What is achieved in 12 years

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University Hospital, Clinic of Pediatric Endocrinology, Varna, Bulgaria

Type 1 still remains the main diabetes entity in children/adolescents in Europe. Its short and long-term management poses considerable difficulties yet. Our aim is to evaluate the diabetes management in a tertiary center (university hospital and affiliated out-patient clinic) and to compare it with previous time-periods. A total of 150 children are under constant care of a team of 2 pediatric endocrinologists, 3 junior doctors, 2 diabetes nurses and a psychologist. The mean age of the patients is 12.6±3.6 years, mean diabetes duration 4.9±3.8 (0.1-14.0) years. On “conventional” treatment (2 daily injections) are 12.3% of the children, compared to 66% in 1995 and 64.3% in 1999, while 4 or more daily insulin application use 76.7% of the children, 65.7% with at least one insulin analogue. The mean hospital stay at diagnosis is 21.3 days in 1986-1988, 14.2 in 1996-1998 and 7.5 in 2007. The number of children visiting the facilities regularly (more than 4 times per year) increases from 20.8% in 1997 to 72.0% in 2007 (p<0.05). Two and more HbA1c investigations per year were performed in 47.3% of the patients, mean value for the trimester under evaluation was 8.76±2.1%, 36% had HbA1c <7.5%. The mean BMI doesn’t differ from the same-age diabetes free population. Initial DKA is present in 33%, the most stable index throughout the years (30.1% in 1997). The relative share of severe hypoglycemia decreases significantly - from 35.7% of all patients (in 1997) to 72.0% in 2007 (p<0.05). Two and more HbA1c investigations per year were performed in 47.3% of the patients, mean value for the trimester under evaluation was 8.76±2.1%, 36% had HbA1c <7.5%. The mean BMI doesn’t differ from the same-age diabetes free population. Initial DKA is present in 33%, the most stable index throughout the years (30.1% in 1997). The relative share of severe hypoglycemia decreases significantly - from 35.7% of all patients (in 1997) to 72.0% in 2007 (p<0.05). Two and more HbA1c investigations per year were performed in 47.3% of the patients, mean value for the trimester under evaluation was 8.76±2.1%, 36% had HbA1c <7.5%. The mean BMI doesn’t differ from the same-age diabetes free population. Initial DKA is present in 33%, the most stable index throughout the years (30.1% in 1997). The relative share of severe hypoglycemia decreases significantly - from 35.7% of all patients (in 1997) to 72.0% in 2007 (p<0.05).
The information obtained with the usual glycemic control in diabetic patients is limited. With the aim to get the 48 hours glucose profile (CGM), we try to analyse pre and postprandial glycemic values and other variables of phenomena by means of glucose sensor Glucoday®, from Menarini Diagnostics. Patients were selected by showing difficulties in having a good metabolic control. Clinical characteristics are reflected in the table:

<table>
<thead>
<tr>
<th>Age onset</th>
<th>Age CGM</th>
<th>Sex</th>
<th>Associations</th>
<th>Complications</th>
</tr>
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<tbody>
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<td>4yrs 7mo</td>
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<td>9yrs 2mo</td>
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<td>15yrs 2mo</td>
<td>male</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>12yrs 7mo</td>
<td>14yrs 9mo</td>
<td>male</td>
<td>CLT</td>
<td>no</td>
</tr>
<tr>
<td>11yrs 7mo</td>
<td>13yrs 4mo</td>
<td>male</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>13yrs</td>
<td>15yrs 5mo</td>
<td>male</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>13yrs</td>
<td>16yrs 2mo</td>
<td>male</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>8yrs 6mo</td>
<td>12yrs 9mo</td>
<td>male</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

In all of them, a catheter was installed in the abdominal wall during 48 hours, and connected to the device to register the corresponding glucose values. Signed consent was obtained in all cases. In the global group, CGM serves to detect abnormal patterns of glycemia. A correct profile was not obtained by the insulinic treatment in spite of supplements with ultra-rapid insulins. In celiac patients, a very irregular pattern was obtained due to the special hyper-glycemic diet. In the case under corticoids treatment, the glycemic profile was very irregular. In one adolescent girl, spurious and not foreseen meals were detected. The continuous glucose monitoring is a useful tool to know if the treatment indicated is correct, to detect errors in the patients’ familiarity and to give a clearer and understanding view of the situation to the parents and the convenience of a more aggressive insulinization in certain cases.

### P2-d3-717 Pancreas 2

#### Leptin levels in children with type 1 diabetes

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**Background:** The possible effects of insulin therapy in Type 1 diabetes on leptin levels are controversial.

**Objectives:** To compare leptin levels in diabetic children with a non-diabetic control group. To evaluate the variables that can affect leptin levels in diabetic children.

**Methods:** We performed a descriptive, cross-sectional study comparing a sample of 172 diabetic children (group A) with a control group of 80 non-diabetic, apparently healthy children (group B). In both groups we assessed gender, age, puberal stage, BMI-SDS for age and gender, and leptin levels. For group A we recorded age at diagnosis, diabetes duration, scheme of insulin therapy, HbA1C and IGF-1 levels.

**Results:** Mean age in groups A and B was 12.1±3.9 and 10.8±4 years, respectively (p = 0.02). Group A had a higher prevalence of boys (52%; n=90) than group B (34%; n=27), p = 0.004. Table 1 presents the results by gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>A group</th>
<th>p</th>
<th>Male</th>
<th>A group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>12.1±3.9</td>
<td>11.4±3.6</td>
<td>ns</td>
<td>12.1±4.4</td>
<td>9.6±4.5</td>
<td>0.008</td>
</tr>
<tr>
<td>BMI</td>
<td>20.7±4.1</td>
<td>18.5±2.5</td>
<td>0.001</td>
<td>20.4±3.4</td>
<td>18.8±3.4</td>
<td>0.03</td>
</tr>
<tr>
<td>sds BMI</td>
<td>0.76±0.1</td>
<td>0.8±0.15</td>
<td>0.0001</td>
<td>0.91±0.87</td>
<td>0.63±1.12</td>
<td>ns</td>
</tr>
<tr>
<td>leptin level</td>
<td>10.9±5.6</td>
<td>16.3±1.15</td>
<td>0.002</td>
<td>3.7±3.4</td>
<td>7.8±7.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

In both groups there was a positive correlation between leptin levels and both BMI and BMI-SDS. Table 2 displays the results by gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>A group</th>
<th>p</th>
<th>Male</th>
<th>A group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.73</td>
<td>0.0001</td>
<td>0.75</td>
<td>0.0001</td>
<td>0.47</td>
<td>0.0001</td>
</tr>
<tr>
<td>sds BMI</td>
<td>0.5</td>
<td>0.0001</td>
<td>0.54</td>
<td>0.0001</td>
<td>0.49</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

In diabetic children, only in girls, did leptin levels show a positive correlation with diabetes duration (r=0.47; p=0.0001), HbA1C (r=0.2; p=0.02) and IGF-1 levels (r=0.38; p<0.0001). When comparing leptin levels between diabetic
Parking

Continuous subcutaneous insulin infusion in a case of glycogen storage disease and type 1 diabetes
Denise Poole, Karen Logart, Julian Raiman, Ahmed Massoud
1 Northwick Park Hospital, Children’s Services, London, United Kingdom; 2 Imperial College London, Department of Academic Neonatal Medicine, London, United Kingdom; 3 University of Toronto, Division of Clinical and Metabolic Genetics, Toronto, Canada

Glycogen Storage Disease (GSD) is a rare genetic disorder. Several types of GSD are now known (type 0 - IX). GSD IX (~1/200,000 live births) results in marked hepatomegaly and fasting hypoglycaemia due to the inability to convert glycogen stores into glucose. We present an unusual case of a child (Y) with GSD IX who subsequently developed Type 1 diabetes mellitus and discuss the difficulties encountered in attaining glycaemic control. Y presented with hepatomegaly, growth faltering and poor dentition at age 2 years and was diagnosed as having GSD Type IX confirmed by genetic analysis. Dietary therapy consisted of uncooked cornstarch, Maxijul and overnight nasogastric feeds. Management was aimed at maintaining normoglycaemia and minimising secondary complications. At age six years, Y developed Type 1 diabetes. He was initially commenced on Mixtard 30/70 and then switched to a basal bolus regimen. Because Y ate meals slowly, hypoglycaemic episodes occurred and a trial of Actrapid Bd with Levemir at night was commenced. As glycaemic control remained poor, continuous subcutaneous insulin infusion (CSII) was introduced empirically. After 12 months of CSII the following was achieved:
- A 30% reduction in Y’s total daily insulin dose
- Reduction in HbA1c from 9.5% to 8.3%
- Improvement in weight (9th to 50th centile)
- Reduction in liver size
- Reduction in rate of mild hypoglycaemia (BGL 2.6 - 4mmol/l) from -3 ± 4 to -0.5 ± 1.1 episodes per night
- Avoidance of severe hypoglycaemia (BGL < 2.6 mmol/l)
- Increase in Y’s energy and activity
- Reduction in parental anxiety

This case exemplifies the difficulties in the management of Type 1 diabetes where another (rare) condition affecting plasma glucose homeostasis co-exists. The use of CSII in a child with GSD and Type 1 diabetes is shown to be beneficial in optimising diabetes glucose control and growth potential.

Poster Presentations

Continuous subcutaneous insulin infusion in a case of glycogen storage disease and type 1 diabetes
Denise Poole, Karen Logart, Julian Raiman, Ahmed Massoud
1 Northwick Park Hospital, Children’s Services, London, United Kingdom; 2 Imperial College London, Department of Academic Neonatal Medicine, London, United Kingdom; 3 University of Toronto, Division of Clinical and Metabolic Genetics, Toronto, Canada

Differences in testicular development between 5-α-reductase-2 deficiency and isolated bilateral cryptorchidism
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1 Kindertagesklinik, Pediatric, Liestal, Switzerland; 2 Cairo State University, Pediatric Surgery, Cairo, Egypt

Background: The majority of patients with steroid 5-α-reductase-2 deficiency (SRD5A2) will develop infertility. This study assessed the hypothesis that infertility development in SRD5A2 subjects is related to 5-α-reductase-2 deficiency rather than the undescended testicular position.

Patients and Method: Eight SRD5A2 patients (12 testes) aged 8 months, 2, 4, 9, 11, 13, 21 and 24 years had testicular biopsy performed during corrective surgery. A second group of 11 patients (11 testes) had identical testicular position and age with orchidopexy for isolated bilateral cryptorchidism had a bilateral testicular biopsy at surgery. Testicular histopathology from the two groups was compared to estimate the negative impact of the undescended position.

Results: Prepubertal SRD5A2 testes had Ad spermatogonia and Leydig cell hyperplasia. In contrast, prepubertal testes of bilateral cryptorchidism, with identical testicular position and age had a bilateral testicular biopsy at surgery. Testicular histopathology from the two groups was compared to estimate the negative impact of the undescended position.

Prevalence of testicular microlithiasis in patients with congenital adrenal hyperplasia
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Testicular microlithiasis(TM) is characterized by calcium deposits within the seminiferous tubules. On ultrasound, TM is seen as multiple, uniform, nonshadowing echogenic foci of 1-3 mm, scattered throughout the testicular parenchyma. TM has been found to be associated with benign conditions (cryptorchidism, varicoceles, infertility, testicular torsion, male pseudohermaphroditism, Kleinfelter’s syndrome, neurofibromatosis) but has also been reported in association with testicular malignancy. The aim of this study was...
to determine TM prevalence on ultrasound in patients with congenital adrenal hyperplasia (CAH). Scrotal ultrasound was performed in 41 patients with CAH. Thirty-one were 21-hydroxylase deficiency(21-OHD) and ten were 11β-hydroxylase deficiency(11β- OHD). Mean age of patients was 12.04 ± 4.8 years (range: 2.5-25.5 years). Twenty patients were prepubertal TM was classified with respect to the number of microliths per ultrasound field as limited(TM) when less than 5 microliths, grade 1, 5-10 microliths, grade 2, 10-20 microliths and grade 3. >20. High frequency linear transducer (12 MHz) was used in all patients and bilateral in 9(21.9%) patients with a mean age of 15.8±5.4 yrs(range:10.8-25.5), 7 patients with 21-OHD and 2 patients with 11β-OHD. Three patients were prepubertal. Four patients(9.7%) had LTM, one patient(2.4%)grade 1, one patient(2.4%) grade 2, three patients(7.3%) grade 3. Bilateral varicocele was found in one of these patients. There were 9 patients with bilateral testicular adrenal rest (TAR). Four patients have TM and TAR together. In conclusions, our study show that TM is frequently found in CAH patients related neither to the age nor to the pubertal status of patients. CAH patients should be followed up both for TAR and TM by ultrasound.

P2-d3-722 Reproductive Endocrinology 2
Ontogenic changes in inhibit B and antimullerian hormone from birth to puberty in patients with complete androgen insensitivity syndrome (CAIS)
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1Hospital de Niños R.Gutierrez, Division of Endocrinology, Buenos Aires, Argentina; 2Hospital de Niños H.Magariños, Centro de Investigaciones Endocrinológicas (CEDIE), Buenos Aires, Argentina

In patients with CAIS, where a functional androgen receptor is absent, a blunted LH pattern is observed after birth, reflecting the importance of the hypothalamic androgen imprinting for the postnatal gonadotropin secretion in males. The regulation of inhibit B (InhB) and Anti-mullerian hormone (AMH) production by Sertoli cells during the prepubertal quiescent period still remains speculative. CAIS might represent a useful model to better understand androgen action on the regulation of these peptides from birth to early puberty. For this reason, we investigated the secretion of InhB and AMH in patients from birth through infancy up to early stages of puberty (Tanner II). Seven 46,XY girls with CAIS (age range:2 days to 9.5 yr) were included in this observational, retrospective study. Levels of LH, FSH, T, Pro-αC, InhB and AMH were determined before gonadectomy. A concomitant increase in InhB(546 and 639 pg/ml) and FSH(1.4 and 2.2 IU/l), levels was observed in two patients, 2-day-old and 5.2 yr, respectively. High InhB (472 and 401 pg/ml) with normal FSH (2.2 and 1.6 IU/l, respectively) levels were observed in two patients at early puberty. Whereas, normal InhB (172 and 146 pg/ml) levels were associated with high FSH (6.9 and 8.8 IU/l, respectively) in two out of three patients during childhood. Pro-C was increased in two patients and InhB/Pro-C ratio was altered in 5 patients. AMH did not always follow variations either in InhB or FSH levels. In conclusion, in the absence of an active androgen receptor there is an abnormal regulation of Sertoli cell peptide secretion. However, lack of a homogenous pattern for this alteration, do not allow establishing the mechanism involved, that still needs to be clarified.

P2-d3-723 Reproductive Endocrinology 2
Peutz-Jeghers syndrome revealed by testicular calcifications and gynecostasia in a pre-pubertal boy
Louise Montagne1; Sylvie Rossignol1; Diane Doummm1; Georges Audry1; Sabah Boudjemaa1; Nadine Hanna1; Florence Renaldo2; Liliane Boccon-Gibod3; Dominique Vidaud3; Irina Netchine3
1Trousseau Children Hospital, APHP, Pediatric Endocrinology, Paris, France; 2Trousseau Children Hospital, APHP, Pediatric Neurology, Paris, France; 3Trousseau Children Hospital, APHP, Pediatric Surgery, Paris, France; 4Trousseau Children Hospital, APHP, Pathology, Paris, France; 5Beaujon Hospital, Molecular Genetics, Clichy, France

A seven years old boy with advanced bone age of 11, no familial history was referred for gynecostasia and suspicion of testicular tumor. He previously had nasal polyps removed. He was 132 cm tall (+2.5 SDS) and weighed 29.8 kg (97 percentile) with an increased growth velocity for his age (10 cm/year). He had a left gynecostasia (1 x 1 cm), bilateral increased testicular length (25 x 30 mm), a slightly stimulated penis, perioral and periocular lentigines. Testicular ultrasound revealed bilateral microcalcifications with a larger calcified mass (5 x 5 mm) in the right testis. Testosterone, LH, FSH were in the normal range ruling out a central precocious puberty. Estradiol and inhibit alpha levels were elevated but inhibit B was normal. Large tumescence of the right testicular mass was performed. Pathological diagnosis was Intra tubular Large Hyalinizing (and Calcifying) Sertoli cell Neoplasia. Peutz-Jeghers syndrome (PJS) was suspected and confirmed by the identification of a deletion encompassing the STK11 gene promoter region and 1st exon. A third generation aromatase inhibitor (anastrazole 1 mg daily) was started at 7.6 years. During the first year of treatment, testicular volume did not change, gynecostasia disappeared and growth velocity decreased (6 cm/year). Bone age progression was of one year only. Estradiol level decreased demonstrating a good biological response to anastrozole. PJS is a rare autosomal dominant cancer predisposition syndrome characterized by mucocutaneous pigmentation and multiple gastrointestinal and (or) nasal polyps secondary to mutation of the STK11 gene. Endocrine manifestations include gynecostasia due to a distinctive Intra tubular Sertoli Cell proliferation (variant of Large Cell Calcifying Sertoli cell tumor = LCCSCT ) producing estrogen and elevated inhibit alpha. LSCSST are also identified in Carney complex, whereas testicular microlithiasis has been reported in Mc Cune-Albright syndrome. Aromatase inhibitors are so far efficient on estrogen levels, gynecostasia and progression of bone maturation.

P2-d3-724 Reproductive Endocrinology 2
Puberty in CHARGE syndrome
Jeremy Kirk; Ellen Stone
Birmingham Children’s Hospital, Endocrinology, Birmingham, United Kingdom

Whilst growth and genital disorders are an integral part of CHARGE syndrome: Coloboma, Heart defect, Chaonal Atresia, Retarded growth and development, Genital and Ear anomalies there are few data on adolescent development. We have investigated 18 patients (9 male) with CHARGE syndrome at a median age of 15.9y. (range 10.6-18.2). Of the boys 5 had micropenis, and 4 undescended testes requiring orchiopexy. 5 patients (all female) showed spontaneous puberty (B2 or testes >4 ml). Median (range) height SDS was -4.1 (-5.2 to -2.6) and 14 (patients 8 female) where gonadotrophins were measured LH was >1 U/l in 3 (all girls), and FSH > 1 U/l in 3 (all girls), and FSH > 1 U/l in 3 (all girls). Post hCG stimulation (N=5) testosterone rose to a mean of 1.02 nmol/l (range 0.5-1.9): only 1 showed a 3-fold rise. LHRR testing in 11 patients (6 female) showed a mean peak (range) of 14.0 (3.2-6.4) U/l in the females and 1.3(0.5-2.6) U/l in males; for FSH was 7.5(3.6-11.6) U/l for females and 2.1(0.9-4.0) U/l for males. In the 7 girls who had a pelvic USS performed; 4 showed a pre-pubertal uterus, and in the 4 the ovaries were either small or not seen. Six females currently receive oestroegen therapy (4 OCP, 1 oral HRT, 1 patch), and 8 are receiving testosterone therapy (im depot in 5, oral in 2). In conclusion, children with CHARGE syndrome are not necessarily short, with approximately 50% having heights within the normal range. Boys with CHARGE show clinical and biochemical evidence of gonadotrophin deficiency, and fail to enter puberty spontaneously, whilst girls with CHARGE show less gonadotrophin imbalance, with delayed/arrested puberty.

P2-d3-725 Reproductive Endocrinology 2
A rare syndrome cause of premature ovarian failure: Blepharophimosis-Ptosis-Epicanthus inversus Syndrome type 1
Bernto Brassard1; Véronique Beauloye1; Winnie Courtens2
1Cliniques Universitaires St. Luc, UCL, Pediatric Endocrinology and Human Genetics, Brussels, Belgium; 2Cliniques Universitaires St-Luc, UCL, Center of Human Genetics, Brussels, Belgium

Introduction: Premature ovarian failure (POF) is characterized by amenorhoea, hypoestrogenism and elevated serum gonadotropins for more than six months in women younger than 40 years. We present a rare genetic cause of
POF, underlining the very specific phenotype of these patients, and discuss their management. **Clinical case:** The propositus is a 2-year-old girl of unrelated healthy Polish parents. The first months of life were marked by slight psychomotor retardation and dysmorphic signs, with mainly bilateral palpebral ptosis. The diagnosis of Blepharophimosis-Ptosis-Epicanthus inversus Syndrome (BPES) was evoked at 1 year of life. This clinical diagnosis was confirmed by genetic analysis retrieving a complete heterozygous de novo deletion of FOXL2 (3q22-23). Pelvic ultrasound was normal. **Discussion:** BPES (OMIM 101000) is an autosomal dominant developmental disorder characterized by malformation of the extra-ocular structures leading to palpebral ptosis, blepharophimosis and variable degree of epicanthus inversus. Two clinical subtypes are known, according to the occurrence (type 1) or not (type 2) of POF, presenting often as progressive secondary amenorrhea after normal puberty. No endocrinological or reproductive dysfunctions were described until now in males. Both types are caused by mutation in the FOXL2 gene, often de novo. This gene codes for a member of the winged-helix/forkhead transcription factors family. It is implicated in extra-ocular muscle formation and ovarian function, probably acting in follicle maintenance with regards to its granulosa-cells localization in humans. It is thought to be one of the earliest known sex-dimorphic markers of ovarian determination/differentiation in vertebrates. So far there is no specific feature to distinguish both types, even if some genotype/phenotype correlations are described (i.e. most severe with possible mental retardation in complete deletions). Ovarian cysts and/or small dystrophic ovaries and uterus have been observed, and complaint-oriented pelvic ultrasound and postpubertal follow-up are requested.

**P2-d3-726 Reproductive Endocrinology 2**

**Hypogonadotrophic hypogonadism and abnormal oocyte bulb development in CHARGE syndrome with CHD7 mutation**

Young-Lim Shig1; Yong-Wha Lee2

1Soonchunhyang University Bucheon Hospital, Pediatrics, Bucheon-si, Republic of Korea; 2Soonchunhyang University Bucheon Hospital, Laboratory Medicine, Bucheon-si, Republic of Korea

CHARGE syndrome is a congenital malformation disorder that includes coloboma, heart defect, choanal atresia, retarded growth and development, genital hypoplasia, and ear abnormalities. Recently hypogonadotropic hypogonadism and abnormal oocyte bulb development are occasionally described in CHARGE syndrome with CHD7 mutation. We report the case of Korean female patient with CHARGE syndrome and CHD7 mutation who had hypogonadotropic hypogonadism and abnormal oocyte bulb as manifested by delayed puberty and growth retardation. This patient was a 13 year old girl who had poor pubertal development and short stature. She was born at 39 weeks of gestation with a birth weight of 3.5 kg. She had ventricular septal defect. She suffered from feeding and respiratory difficulties at first year. She showed failure to thrive. She had severe mental retardation and autistic-like behavior. Her developmental quotient was assessed as 36 by the KEDI-WISC test. She had both optic nerve coloboma. External ear abnormalities and hearing loss were observed. In CT scanning of the temporal bones, bilateral agenesis of the semicircular canals were demonstrated. We identified a heterozygous nonsense mutation at exon 20 of the CHD7 gene. c.4601G>A; W1534X. Her height was 129cm (-2.6 SD) when examined at the age of 13 years. She had absence of pubertal development. A GnRH test showed prepubertal responses of LH (basaline 0.51 mIU/mL and peak 0.54 mIU/mL) and FSH (baseline 0.02 mIU/mL and peak 1.16 mIU/mL). A hypoplastic uterus and small sized both ovaries were found by pelvic MRI. Brain MRI showed aplasia of the right and hypoplasia of the left olfacotory bulb and bilateral absence of the olfactory sulci. Treatment with estrogen resulted in female secondary sexual development. In adolescent patients with CHARGE syndrome, growth retardation and delayed puberty has caused a lot of concerns. Therefore hypogonadotropic hypogonadism with normal oocyte bulb development should be considered as a common finding and needed to be detected earlier for growth and pubertal development.

**P2-d3-727 Reproductive Endocrinology 2**

**Timing of pubertal onset in girls: Evidence for non-Gaussian distribution**

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The timing of the onset of puberty is considered to approximate a normal distribution. However, it is a general impression among clinicians that many girls—but much fewer boys—present with secondary sex characteristics at a younger age than normal. Furthermore, many more girls present with early than late puberty. This led us to hypothesize that the distribution of the timing of the onset of puberty in girls might have changed, i.e. it might be skewed to the left. Aim of the study was to examine the distribution of the timing of the onset of puberty in normal girls. Onset of puberty, i.e. breast development (B2), was studied longitudinally in 311 schoolgirls aged 6.4-8.2 years, while the girls were prepubertal, until the onset of puberty. We also studied cross-sectionally the pubertal development of 1032 girls, 6 to 14 years old. In the longitudinal study median of the distribution of age at B2 was 10.0 years (25th and 75th centiles were 9.2 and 10.6 years, respectively). Skewness was -0.45 (p<0.001), suggesting a negatively skewed distribution. In the cross-sectional study, 126 subjects were found at B2. Median of the distribution of age at B2 was 10.1 years (25th and 75th percentiles were 9.7 and 11.2 years, respectively). Skewness was -0.44 (p<0.03), also suggesting a negatively skewed distribution. In the longitudinal study the earliest age that a girl presented breast development was 7.0 and the latest 12.1 years. The 3rd and the 97th centile for the onset of puberty in the longitudinal study were 7.5 and 11.7 years, respectively, and in the cross-sectional study were 6.5 and 12.7 years, respectively. Taken together these data suggest that the cut-off stages for precocious or delayed puberty in girls, at least in our population, may be set at 7.5 and 12.5 years, respectively. In conclusion, our data suggest a non-Gaussian distribution in the age at onset of puberty in girls. The currently used cut-off ages for precocious and delayed puberty may not be applicable to modern children, therefore up-to-date studies on pubertal maturation are needed.

**P2-d3-728 Reproductive Endocrinology 2**

**CD95 and TRAIL induced lymphocytes apoptosis in girls with precocious puberty**

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1University of Palermo, DUMI, Palermo, Italy; 2University of Pisa, Pediatric Endocrinology, Division of Pediatrics, Pisa, Italy; 3University of Palermo, Department of Surgical and Oncological Disciplines, Palermo, Italy

Patients with precocious puberty present significant changes in somatic and psychological development, induced by estrogens and testosterone secretion. Estrogens protect lymphocytes from apoptosis. Recent studies on mice lymphocytes demonstrate a protection of estrogens against apoptosis Fas-FasL pathway. These data could partially explain why autoimmune diseases are more frequent in females, whereas males have higher mortality associated with infectious diseases. We selected ten girls (age: 4-7 years) affected by idiopathic precocious puberty, with pubertal stage B3-PH3-4, increased bone age and growth velocity, echographic signs of ovarian and uterine maturation, increased FSH, LH and 17β-estradiol levels. We also evaluated 10 control subjects without precocious puberty. We studied apoptosis of peripheral lymphocytes using the technique of strafification on Ficoll. Lymphocytes sensitization to apoptotic death mediated by receptors CD95 and TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) was induced. Lymphocytes were incubated for 24 hours with 1 1 ng/ml of PHA and for 4 days with 25U/ml di IL-2. Therefore 2x105 lymphocytes were cultured in 96-well plates and incubated for 24 hours with 200 ng/ml of CD95, 800 ng/ml of TRAIL and with negative control medium alone. Apoptotic death was detected by MTT and lecture by Orange Acridine. With both the inducers we relieved a...
reduced lymphocytes apoptosis versus lymphocytes of control subjects. Our results propose considerations about the immune response and the potential incidence of autoimmune diseases in children with precocious puberty.

P2-d3-729 Reproductive Endocrinology 2
High prevalence of Cyp 21 heterozygous mutation in a group of 26 girls with premature pubarche
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Premature pubarche (PP) is common in girls but its aetiology is often unknown. It is important to recognise this condition since long-term sequelae are beginning to be observed. A non classical 21 OH deficiency can be identified in some cases but the heterozygous (HTZ) condition has not been clearly evaluated. This work was undertaken to determine the prevalence of heterozygosity for 21 OH in premature pubarche girls. We investigated 26 girls with isolated PP. The mean age at diagnosis was 6.8 ± 0.8 years. Endocrine investigations included evaluation of basal plasma testosterone (T) and 17 OH progesterone (17OHP) as well as 17OHP and 21 desoxycorticisol during ACTH testing. Molecular biology of the 21 OH gene was performed in girls with significant elevation of 21 desoxycorticisol (> 400 pg/ml) suggesting 21 OH gene HTZ. The results are listed in the table.

Among the 26 girls with PP, we identified 5 girls with elevated 21 desoxycorticisol; they were heterozygous for 21 OH gene mutation. Two girls presented an abnormal high basal plasma 17 OHP level that corresponds to a 21 OH late onset defect. Our data show that in an homogenous group of PP girls, 21 OH gene abnormalities were present in 7/26 (19%) of cases: HTZ was significantly higher (19%) than in the general population (2%). Although we did not find any difference in the plasma T level between HTZ and non HTZ girls, it is likely that this condition is responsible for the premature adrenarche. In addition, genotyping of these adolescent girls could prevent a potentially severe form of congenital adrenal hyperplasia in offspring.

P2-d3-730 Reproductive Endocrinology 2
Early puberty onset still continues
Beatriz Garcia Cuartero1; Amparo Gonzalez Vergara2; Elena Frias Garcia1; Celina Arana Carledo-Arreguelles3; Elisa Diaz Martinez2; Dolores Tolmo2; Maria Teresa Muñoz Calvo2
1Severo Ochoa Hospital, Pediatrics, Leganés, Spain; 2Area, Pediatric, Leganés, Spain; 3Niño Jesus Hospital, Pediatrics, Madrid, Spain

Changes in timing of puberty have been described in the last years, particularity in girls.

Aim: To determine pubertal trends in children of the Mediterranean area.

Methods: Longitudinal study of 305 caucasian children from May 2002 to May 2007. In boys, the first sign of puberty, Tanner Stage 2, was a testicular volume > 4 ml. In girls, appearance of breast buds development defined Tanner stage 2. We analysed birth weight (BW), weight (kg), height (cm) and body mass index (BMI) (%) in different puberty stages, bone age at stage 2 and at the end of puberty, duration of pubertal growth and pubertal height spurt.

Results: Mean age (years) (SD) for girls stage 2 was 10.1 (1.4), with a bone age of 10.3 (1.1). For boys stage 2 was 12.4 (1.5) with a bone age of 11.9 (1.3). Age at menarche was 12.0 (1.3) with a bone age 13.2 (0.9). For boys stage 5: 15.6 (1.5) with a bone age of 14.5. Duration of puberty growth for girls was 2.5 years (1.1) and for boys 3 years (1.2). Pubertal height spurt in girls was 15.7 cm (5.0) and for boys 19.5 (7.6). Girls with puberty onset < 9 years of age show a greater pubertal height gain 19.7 cm (4.3) than girls > 9 years of age 14.4 (4.5) (p<0.0001) and a longer period of pubertal growth 3.1 years (0.8) versus 2.3 (0.9) (p<0.0001).

Conclusions: Girls present secondary sex characteristics and menarche at a younger age than previous studies in the Mediterranean area. Bone age correlates with chronological age for both sexes at the beginning of puberty but not at the end. In girls early onset of puberty was associated with a greater pubertal height gain and a longer period of pubertal growth. There was no correlation between BW or BMI with onset of puberty.

P2-d3-731 Reproductive Endocrinology 2
Central precocious puberty in a patient with adrenal hypoplasia congenita
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1University of Wales, Paediatric Endocrinology, Cardiff, United Kingdom; 2University Hospital of Wales, Medical Genetics, Cardiff, United Kingdom

We report the case of a 2.5 year-old Caucasian boy with X-linked Adrenal Hypoplasia Congenita (AHC) who developed central precocious puberty at 6 months old. He was born at term weighing 3.7kg and is the eighth child of a known carrier of a DAX-1 gene deletion. Two other siblings were also affected, one died from adrenal crisis at 10yrs. Molecular genetic analysis confirmed the familial DAX-1 mutation. Replacement hydrocortisone, fludrocortisone and sodium supplements were initiated at 1-week of age. He remained well apart from gastro-oesophageal reflux and intercurrent viral illnesses. At 5 months old, clinical signs of virilisation were noticed: P2, G2, Testicular volume (TV) 1ml. His length accelerated from the 25th to the 75th centile and his pubertal stages progressed to P2, G3, TV 5mls over the next 9 months. Testosterone level was raised for his age (8nmol/l) and GnRH stimulation test was compatible with central puberty (Table). Normal adrenal androgen levels (deoxycorticisol <2.4nmol/l, DHEA <0.2umol/l, progesterone <2nmol/l, androstenedione <0.5mol/l, 17-OHP 1.5mmol/l and testicular hyper-responsiveness to prolonged âhCG test (stimulated testosterone 75.4nmol/l) demonstrated raised testosterone levels that were testicular in origin. An appropriately suppressed timed ACTH profile (ACTH<10ng/l) and early morning renin level (3.2pmol/ml/h) confirmed adequate steroid replacement. GnRH analogue therapy was initiated and repeat baseline gonadotrophins 4 months into treatment showed adequate pubertal suppression. Table: Gonadotrophin Results (pre-treatment & 4 months post-treatment)

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>5</th>
<th>5</th>
<th>17</th>
<th>17</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>LH</td>
<td>FSH</td>
<td>Testosterone (pmol/l)</td>
<td>LH</td>
<td>FSH</td>
</tr>
<tr>
<td>0</td>
<td>5.4</td>
<td>0.7</td>
<td>8.0</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>30</td>
<td>11.6</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>11.1</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although usually associated with hypogonadotropic hypogonadism, cases of ACTH dependant and gonadotrophin independent precocious puberty with AHC have been reported. Our patient, developed gonadotrophin dependant precocious puberty that was independent of ACTH and responded well to GnRH analogue treatment.

P2-d3-732 Reproductive Endocrinology 2
Comparison of three doses of Leuprolide Acetate in the treatment of central precocious puberty
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1Institute of Maternal and Child Research, Faculty of Medicine, University of Chile, Santiago, Chile; 2Institute of Maternal and Child Research, University of Chile, Santiago, Chile

Depot GnRH analogs (GnRHa) have been widely used for the treatment of central precocious puberty (CPP). Adequate gonadotropin suppression halts pubertal progression and decelerates skeletal maturation induced by prema-
treme exposure to steroids, allowing maintenance of growth potential. The optimal doses to obtain hormonal suppression are still unknown, especially in patients with higher weights. The goal of our study was to evaluate and compare the efficacy of three Leuprolide Acetate (LA) preparations, suppressing gonadotropin secretion in girls with CPP. In an open 12 month protocol, we evaluated LA 7.5 mg/month, 11.25 and 22.5 every 3 months in 15 patients (14/1 female/male) with CPP and weights over 30 kg. The diagnosis was supported by physical exam (pubertal stage) and a GnRH-stimulated LH peak > 6 IU/ml by IRMA. Clinical follow-up, bone age, pelvic ultrasound and GnRH test and LH, FSH 40 minutes post analogue administration were performed periodically. Ultra sensitive estradiol levels were measured after 6 and 12 months of treatment. Clinical findings and hormone levels are shown as mean ± SEM in Table 1. Data was analyzed using ANOVA, Kruskal-Wallis and non-parametric Wilcoxon tests. GnRH-stimulated LH peak < 2 IU/ml, the main efficacy criterion was met in 80, 60 and 100% of the children at 9 months in the 7.5, 11.25, 22.5 mg doses respectively. The general tolerance to the three preparations was comparable.

<table>
<thead>
<tr>
<th>dose</th>
<th>7.5 mg</th>
<th>11.25 mg</th>
<th>22.5 mg</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.5 ± 0.2</td>
<td>9.1 ± 0.4</td>
<td>9.2 ± 0.3</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td>1.39 ± 0.31</td>
<td>1 ± 0.4</td>
<td>0.73 ± 0.36</td>
<td>0.453</td>
</tr>
<tr>
<td>Basal LH 0m (U/ml)</td>
<td>1.4 ± 0.49</td>
<td>1.17 ± 0.41</td>
<td>2.35 ± 0.41</td>
<td>0.416</td>
</tr>
<tr>
<td>Peak LH 0m (U/ml)</td>
<td>13.2 ± 3.3</td>
<td>11.6 ± 3.1</td>
<td>19.4 ± 5.6</td>
<td>0.403</td>
</tr>
<tr>
<td>40 min LH 0m (U/ml)</td>
<td>22.4 ± 2.14</td>
<td>23.9 ± 7.9</td>
<td>41.8 ± 15</td>
<td>0.507</td>
</tr>
<tr>
<td>Peak LH 9m (U/ml)</td>
<td>0.74 ± 0.2</td>
<td>1.32 ± 0.28</td>
<td>1.05 ± 0.15</td>
<td>0.001</td>
</tr>
<tr>
<td>40 min LH 9m (U/ml)</td>
<td>1.19 ± 0.35</td>
<td>2.3 ± 0.78</td>
<td>1.37 ± 0.19</td>
<td>0.001</td>
</tr>
<tr>
<td>% LH &lt; 2U/ml 9m</td>
<td>80</td>
<td>60</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

These results suggest that the 3-month 22.5 mg LA more efficiently suppresses the gonadotropin secretion in girls over 30 kg compared with the 11.25 mg LA preparation and it is a satisfactory alternative for the therapy of children with CPP.

P2-d3-733 Reproductive Endocrinology 2
Aromatase inhibitors resolve hypogonadotropic hypogonadism and significantly reduce body weight in Prader-Willi syndrome

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Prader-Willi syndrome (PWS) is a genetic disorder characterized by dysmorphic features, obesity, hypotonia, mental retardation, often premature adenarche and hirsutism. The type of hypogonadism in PWS, central or peripheral, remains unclear as recent studies support a combined hypothalamic and peripheral mechanism, whilst other recent reports show an intact mini-pituitary gland with normal gonadotropin response. We included a boy with PWS at the age of 13.2 years. He presented since the age of 5 yrs premature adenarche and morbid obesity. Genetic studies showed maternal uniparental disomy of chromosome 15q11-13. He measured 144.5 cm (-1.73 SDS), weighed 72.9 Kg (+2.19 SDS) -unchanged the last 3 yrs-, his BMI was 34.9 Kg/m2 (+3.28 SDS) and his bone age 15.8 yrs. Predicted adult height was 147.9 cm with a target height of 179 cm. At presentation he was hypogonadotic with testes barely palpable (both < 1 ml), but with normal penile length for pubertal stage. He showed normal response of 17-OH-progesterone to ACTH test, no response to LHRH stimulation (peak LH 0.8 and FSH 1.2 mIU/ml), complete GH deficiency and normal response of 17-OH-progesterone to ACTH test, no response to LHRH test and LH, FSH 40 minutes post analogue administration were performed periodically. Ultra sensitive estradiol levels were measured after 6 and 12 months of treatment. Clinical findings and hormone levels are shown as mean ± SEM in Table 1. Data was analyzed using ANOVA, Kruskal-Wallis and non-parametric Wilcoxon tests. GnRH-stimulated LH peak < 2 IU/ml, the main efficacy criterion was met in 80, 60 and 100% of the children at 9 months in the 7.5, 11.25, 22.5 mg doses respectively. The general tolerance to the three preparations was comparable.

P2-d3-734 Reproductive Endocrinology 2
High prevalence but different hormonal profiles of hyperandrogenism among obese or type 1 diabetic adolescents

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1 Hôpital Necker Enfants-Malades, Pediatric Endocrinology Diabetology and Gynecology, Paris, France; 2 Hôpital Necker Enfants-Malades, Obesity and Nutrition Pediatric Unit, Paris, France; 3 Hôpital Robert Debré, Pediatric Endocrinology and Diabetology, Paris, France; 4 Hôpital Necker Enfants-Malades, Pediatric Endocrinology Diabetology and Gynecology, Paris, France

Background: The prevalence and predisposing factors of hyperandrogenism are not well established among obese and type 1 diabetic (DM1) adolescents.

Aims: To define in DM1 and obese adolescents the timing of puberty, the prevalence and factors of hyperandrogenism. Patients: We included 92 obese and 70 DM1 patients, from 12 to 17 years old. We collected data on their puberty and menstruations, evaluated hyperandrogenism by measuring hirsutism via the Ferriman score and measured serum androgens (testosterone, delta 4 androstenedione (Δ4) and Sex-Hormone Binding Globulin (SHBG)). We excluded secondary hirsutism and other pubertal disorder causes.

Results: The age of puberty and pubarche were in the normal range in both groups. 34% of the obese patients had an hirsutism, higher than the 8% figure of the normal population. There was a significant difference in the testosterone (p=0.003), A4 levels (p=0.01) and SHBG levels was lower but not significantly (27.7±21 vs 32±19.3 nmol/l) between obese with and without hirsutism. 38% of the obese patients had irregular menstruations. Those correlated positively with the body mass index (BMI), the testosterone levels, and negatively with the SHBG serum values. 17% of the DM1 patients had a hirsutism with a higher BMI, A4, SHBG (71.6±38.7 vs 54.1±23.3 nmol/l) and testosterone (p=0.03) levels. 33% of the DM1 patients had menstruations dysfunction. Those correlated positively with the insulin dose administered, the testosterone, A4, and SHBG levels. SHBG levels differ between the obese and the DM patients, with hirsutism (p=0.05).

Conclusion: Hirsutism and menstrual cycle disturbances prevalence is increased in our cohort of DM1 and obese adolescents in comparison with the normal population. The hyperandrogenism hormonal profile differ between the two groups of patients, the decreased in the serum SHBG levels playing a major role in obese but not in DM1 adolescents.

P2-d3-735 Reproductive Endocrinology 2
Mayer-Rokitansky-Kuster-Hauser syndrome: An unexpected diagnosis in a young girl with precocious puberty

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Mayer-Rokitansky-Kuster-Hauser syndrome (MRKHs) is an uncommon variation in the prenatal development of the female genital tract. Its features include absent or very short vagina and a uterus that can be absent or immaturely formed. The normal external appearance of MRKH females makes it difficult to diagnose until puberty, when a girl consults a physician because she has not started to menstruate. Therefore the average age of diagnosis is between 15 and 18 years. Occasionally a girl may be diagnosed at birth or during childhood because of other health problems that required abdominal and pelvic ultrasound examination. We present a rare case of MRKHs early diagnosed in a young girl (7.9 yrs old) referred at our outpatient department for premature appearance of thelarche and persistent abdominal pain. Her urological evaluation showed: height-sds +2.2; BMI-sds +1.8; pubertal stages B2, PH 2; the skeletal age was moderately advanced (10.5 yrs, GP method). LHRH test demonstrated a typical pubertal response with a LH peak of 33.9 IU/l while the basal endocrine evaluation was in the normal range for age. On pelvic ultrasound ovaries volume was adequate for pubertal stage but uterus and upper vagina were absent. These data was confirmed by pelvic magnetic resonance (MR). Renal and or skeletal abnormalities were absent.
Neurofibromatosis (NF) which is a genetic disorder affecting the skin and the nervous system is the consequence of an abnormality of neural crest differentiation and migration during the early stages of embryogenesis. Genitourinary NF is a rare condition and clitoromegaly and penile growth due to plexiform neurofibromas have been reported only in a few patients. We report a 6 year-old boy who was investigated for macrogenitalia and diagnosed as genitourinary NF. It has been learnt that his father had NF. On physical examination, 6 cafe-au-lait spots over his entire body, each measuring more than 1.5 cm in diameter and axillary freckling has been detected. On genital examination penile size was 10x3 cm and testes were bilaterally enlarged. (right testes and left testis: 15 ml). Pubic hair was Tanner Stage 1 and no axillaries hairs were present. Prepubertal levels have been determined in hormonal analysis before and after LHRH testing. Plexiform neurofibromas have been detected in penis and scrotal biopsy. The patient had also chronic renal failure because of obstruction of urethral channel due to neurofibromatosis of posterior urethral valve which lead to bilateral hydromephrosis. In conclusion, although NF is a rare reason of macrogenitalia, it should be thought in the differential diagnosis of pseudo precocious puberty in boys.
development. A LH at 30 minutes > 4.4 IU/L is highly predictive of CPP. We propose to limit the hormonal investigation of CPP to a 30 minute GnRH LH stimulated value, since this value was found to be as discriminative as peak LH value observed during the 2 h test.

**P2-d3-739 Reproductive Endocrinology 2**

**Distinguishing features of thelarche variant: evaluation of 93 girls with premature breast development**

Cenzig Kara; Belgin Usta; Alev Oguz Kutlu

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Three groups of girls with premature breast development were studied retrospectively. We tried to identify clinical and hormonal parameters that could distinguish between isolated premature thelarche (IPT), thelarche variant (TV) and central precocious puberty (CPP). The initial evaluation of 93 girls with isolated breast enlargement before age 8 included determination of chronological age (CA), bone age (BA), pubertal stage, auxological data, pelvic ultrasonography, and gonadotropin responses to GnRH stimulation test. Patients with pubic hair or vaginal bleeding and peripheral PP, and followed-up less than 1-year period were rule out from study. CPP was diagnosed according to all of the following criteria: advanced BA (> 2 SD for CA), accelerated height velocity (HV > 1 SD score), and GnRH stimulation test characterized by LH-predominant response (peak LH > 15 IU/L and peak LH/FSH > 1 for RIA, or peak LH > 25 IU/L and peak LH/FSH > 0.35 for ICMA). Diagnostic criteria for IPT were normal BA, normal HV, and FSH-predominant response. Patients who did not completely meet the inclusion criteria for both groups were considered as having thelarche variant. During at least 1-year follow-up, patients showing an acceleration of bone maturation (ABA/ACA > 1.2) and/or HV were performed the second GnRH test. The patients were divided into three diagnostic groups according to the ultimate clinical and hormonal findings: IPT (n: 62; 66.7%), TV (n: 15; 16.1%), and CPP (n: 16; 17.2%). Clinical and hormonal characteristics of the patient groups were given at the table. Clinical characteristics of thelarche variant (also called slowly progressive CPP) and TV are so similar that it may be difficult to distinguish them on the basis of clinical findings. On the other hand, girls with TV show FSH-predominant response to GnRH stimulation, as seen in girls with IPT. In conclusion, thelarche variant differs from CPP and IPT owing to FSH predominance and systemic estrogen effects such as growth acceleration or BA advancement, respectively.

**P2-d3-740 Reproductive Endocrinology 2**

**Pubertal development in young girls in North Italy**

Gianni Russo; Paolo Brambilla; Marco Pita; Roberto Marinnello; Marina Picca; Matilde Ferrario; Giuseppe Chiumello

1RCS San Raffaele, Department of Pediatrics, Endocrine Unit, Milan, Italy; 2FIMP Lombardia, Dipartimento Formazione Permanente, Milan, Italy; 3Vita-Salute San Raffaele University, Department of Pediatrics, Endocrine Unit, Milan, Italy

The timing of normal pubertal development (PD) in females has received increased attention for several years over the past. Studies in the United States (US) showed a further and still evolving decrease in age of puberty onset. Aim of our study was to describe secondary sexual characters in a large population of 2 to 14 yr old girls from Northern Italy to define physiological puberty timing. This is a cross-sectional study conducted by Family Paediatrician (FP) between September 2005 and November 2006 in Lombardia, a North Italy region. Patients were girls from 2 to 14 yr of age who spontaneously requested a clinical evaluation for routine health checkups or acute illness. Exclusion criteria were adoption and expressed refusal. A complete physical examination was performed; pubertal status was evaluated following Tanner’s criteria. Breast development staging was done by manual evaluation of mammary tissue. Mean ages and SD of entry into each stage were estimated by probit analysis. The mean age for thelarche is 9,75 yr, for pubarche 10,1 yr, for menarche 12,49 yr, appearing 1,4 yr, 1,6 yr and 1 yr respectively earlier than in Marshall and Tanner’s British population. We noticed a longer time from B2 (9,75 yr) to menarche (12,49 yr; SB2-menarche 2,74 yr) and from B2 to B3 (1,46 yr). The mean age of menarche of subjects and their mothers showed no significant difference. At age 6-11 yr the presence of thelarche and pubarche was significantly more evident in girls with higher BMI. The girls studied present earlier clinical signs of PD in comparison to the current classical definitions. Thus, the age of menarche doesn’t seem to anticipate. Maybe there is a different way of progression of PD, in which the shift to B3 has got more clinical relevance. It is important to define the timing of puberty in every country to establish a correct Public Health policy, for clinical management and to find the causes of early onset and its consequences. The relationship between BMI and earlier onset of puberty could be an example.

**P2-d3-741 Reproductive Endocrinology 2**

**Height outcome of GnRH agonist treatment in girls with abnormal puberty**

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Faculty of Medicine, Chulalongkorn University, Department of Pediatrics, Bangkok, Thailand

GnRH agonist has been proved to be beneficial in terms of final height outcome in precocious puberty girls whose onset before 5-6 years of age. However, treatment in early normal puberty with GnRH agonist is controversial. Thirty-four precocious puberty and twenty-four normal early puberty girls who had been treated with GnRH agonist were retrospectively reviewed. Precocious puberty girl is defined as one with breast development before 8 years of age. Normal early puberty or advanced puberty girl is defined as one with breast development between 8-9 years of age or menarche between 9 to 10 years of age. GnRH agonist 3.75 mg was injected intramuscularly every 4 weeks. Bone age was evaluated by method of Greulich&Polye and then predicted adult height (PAH) was calculated.

<table>
<thead>
<tr>
<th>Precocious Puberty Girls (n=34)</th>
<th>Early Puberty Girls (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (yr)</td>
<td>8.28 ± 1.24</td>
</tr>
<tr>
<td>BA (yr)</td>
<td>10.71 ± 1.56</td>
</tr>
<tr>
<td>Breast onset (yr)</td>
<td>6.9 ± 0.6</td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
<td>8.7 ± 0.9</td>
</tr>
<tr>
<td>Treatment period (yr)</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>Mid-parental Ht (cm)</td>
<td>155.5 ± 3.8</td>
</tr>
<tr>
<td>PAH at start (cm)</td>
<td>150.0 ± 7.4</td>
</tr>
<tr>
<td>PAH at stop (cm)</td>
<td>155.3 ± 6.2</td>
</tr>
<tr>
<td>Final Ht (cm)</td>
<td>156.0 ± 5.9</td>
</tr>
</tbody>
</table>

Treatment with GnRH agonist significantly improve final height in precocious puberty girls compared with PAH before treatment which is similar to other previous studies. From this study, we demonstrated that manipulation of puberty with GnRH agonist also significantly improve final height in normal early puberty girl.

**P2-d3-742 Reproductive Endocrinology 2**

**Selected auxological aspects of anorexia nervosa in pubescent girls - Relations of body weight to body height and menstrual cycle**

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12nd Faculty of Medicine, Charles University, Paediatric Clinic, Praha, Czech Republic; 22nd Faculty of Medicine, Charles University, Information Systems, Praha, Czech Republic; 2nd Faculty of Medicine, Charles University, Clinic of Paediatric Psychiatry, Praha, Czech Republic

Specific aspects of therapy of eating disorders (ED) in pubescent and adolescent girls are related to severe malnutrition at the time of unfinished biological development. The authors concentrated at several issues: 1) exact determination of recommended body weight on the basis of the exact analysis of the weight history (target weight, weight for discharge)
2) relation between body weight and menstrual cycle (menarche, primary or secondary amenorrhea and remenorrhea).

3) risk of non-realization of the genetic growth potential (status of linear growth and skeletal maturity).

Based on analysis of 90 hospitalized patients with anorexia nervosa (34 premenarchal, 56 postmenarcheal, median age 13.8 years) we suggest algorithms for determination of recommended target weight depending on skeletal and sexual maturity: 

- to premenarcheal girls with primary amenorrhea and with indicators of perimenarcheal situation we recommend reaching at least the 25th percentile of weight (BW) for height (BH) and we set the minimum discharge weight at the 10th percentile of BW/BH. (Average at menarche is the 50th percentile BW/BH)
- to postmenarcheal patients with secondary amenorrhea we recommend reaching the 20th percentile of weight for height (for remenorrhea, it is necessary to reach 90 % of appropriate weight or to BMI over 18.5) and we set their discharge weight at the 15th percentile of BW/BH
- for premenarcheal girls with finished linear growth we sum our findings with differentiated recommendations for short (160 cm), average (167 cm) and tall (173 cm) girls.

We strongly emphasize the importance of exact analysis of growth and weight history and of reflection of biological age in girls with eating disorders for successful and reasonable realimentation therapy (traditional backbone of ED therapy).

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**P2-d3-743** Reproductive Endocrinology 2

**Extreme precocious puberty and septum pellucidum cyst**

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A 5 month old girl was referred for pubertal evaluation with Tanner stage II since birth. She was born after 40 weeks gestation and an amniocentesis was performed at 28 weeks because of hydramnios and hypertrophic genitals: karyotype was normal 46XX. At 5 month, she presented tall stature, height was 69 cm (+3SD) with accelerated growth velocity, weight 7.490 (+1SD). Hypertrophic labia majora and minora and normal clitoris was noticed without “café au lait” spots. Serum estradiol level were elevated (54 pg/ml), after LHRR stimulation peak LH response was at 1.7 mU/ml and FSH at 6.1mU/ml, adrenal hormones were normal. Pelvic ultrasonography showed increased ovarian volume (4.6 cm3; 5.5 cm3), and uterus lenght (47 mm) volumes, bone mineral density (BMD) were normal. Serum estradiol level was 15.6 ng/ml, FSH 1.29 IU/ml, LH 2.4 IU/ml, prolactine 2.9 ng/ml and LH/FSH ratio 2.5. This case was considered as a typical case of central precocious puberty (CPP). MRI was performed with cysto-ventriculostomy, showing an arachnoidocele that compressed anterior pituitary lobe against the floor of pitaluitary sella. Ophthalmologic tests were all unremarkable. Treatment with LHRH agonist was administered for two years, the boy is reviewed twice a year, and MRI testing performed every two yeras. Statural and pubertal growths are normal. This case is rare. Primary empty sella syndrome has been reported in association with various pituitary endocrinopathies, exact mechanism leading to CPP remains unknown. Whether this hypothalamic anatomical malformation leads to suppression of inhibitory inputs to GnRH neurons in affected children remains to be determined. Absence of long-term outcome studies explains our attitude, with annual pituitary function testing.

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**P2-d3-744** Reproductive Endocrinology 2

**Primary empty sella syndrome and central precocious puberty in a boy**

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Central precocious puberty (CPP) defined as occurrence of secondary sexual characteristics before age 8 years (girls) and 10 years (boys) is relatively frequent (1/5000 to 1/10000) and context in girls. In boys PP is secondary to a lesion in 80 to 95% cases so that CNS tumours are feared causes. Primary empty sella as cause of PP is rare with only few cases reported. We report a new case to remind clinicians of its existence. A, born on 05/01/1992 was referred at age 10 years 4 months for signs of PP evolving since over a year. Personal history revealed migraines, mother was migranous, and one elder sister had been treated for CPP. Upon clinical examination, height 143.2 cm (+1.09SD french curves), weight 37 kg (BMI 18 kg/m²), BP 100/70 mm Hg, pubertal stage A1P2-3G2-3, testicular length 3.7 X 2.3 cm, in favour of PP. Endocrine work up: LHRH test basal FSH 8 U/l, peak 14.7 U/l, basal LH 3.4 U/l, peak 37.7 U/l, LH/FSH ratio 2.5, plasma testosterone 15.8 mnmol/L, delta-4 androstenedione 3.1 nmol/L (N 1.5 - 17), S-DHEA 1104 nmol/L (N 2600 - 4000), 17(OH)P normal, morning cortisol 301 nmol/L, TSH 1.92 mUI/L, FT4 13.9 pmol/L, Prolactine 4.7 ng/ml (N 2.2 - 8.6), plasma electrolytes normal, GH normal, BA 12 years (Gruelich & Pyle). Head MRI showed presence of an arachnoidocele that compressed anterior pituitary lobe against the floor of pituitary sella. Ophthalmologic tests were all unremarkable. Treatment with LHRH agonist was administered for two years, the boy is reviewed twice a year, and MRI testing performed every two yeras. Statural and pubertal growths are normal. This case is rare. Primary empty sella syndrome has been reported in association with various pituitary endocrinopathies, exact mechanism leading to CPP remains unknown. Whether this hypothalamic anatomical malformation leads to suppression of inhibitory inputs to GnRH neurons in affected children remains to be determined. Absence of long-term outcome studies explains our attitude, with annual pituitary function testing.

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**Assessment of serum leptin and anterior pituitary hormones among Thalassemic females during puberty**

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Growth retardation and short stature are frequent features of Thalassemic children. These features represent critical physical and mental strains that necessitate through study. Assessment of serum leptin, FSH, LH among Thalassemic females during pubertal years, together with assessment of the prevalence of short stature, pubertal delay and the quality of life of these Thalassemic girls were the main aim of this study. Ethical committee approved this study. The study included 28 thalassemia major females aged 10-18 years attending the outpatient pediatric hematology clinic, Suez Canal University Hospital. Twenty eight normal females matched for age volunteered to act as control group. Through history taking, anthropometric measurements, pubertal assessment using Tanner classification, quality of life assessment using Pediatric Quality of Life Inventory version 4 and laboratory assessment of leptin, FSH, LH were performed. Short stature was detected in 35.7% of Thalassemic females, while 25% had normal puberty. Mean serum leptin level was 2.89±1.6 ng/dl compared to 9.11±7.5 ng/dl in the controls. Non significant weak positive correlation between leptin level and body mass index was detected in Thalassemic females while the correlation was significant and strongly positive in the control females. The mean serum FSH was 1.64±1.6 IU/I in Thalassemics compared to 2.66±1.8 IU/I in the controls (p=0.04), while the mean serum LH was 1.49±2.94 IU/I in the diseased females compared to 5.04±7.2 IU/I in the control group (p=0.02). Physical, Social, emotional and school functions were significantly deranged in Thalassemic girls. It was concluded that a significant deranged puberty, short stature and low levels of serum leptin, FSH and LH were detected in Thalassemia major females when compared to a matched control group. Thalassemia females suffered from delayed puberty and poor quality of life probably as a sequelae of their disease.
Hepatoblastoma is the most common malignant liver tumor in early childhood. Most patients are younger than 3 years old with an enlarging asymptomatic abdominal mass. Some patients have fever, pain, anorexia, weight loss. Hepatoblastoma can be associated with precocious pseudopuberty (PP). Penile and testicular enlargement without pubic hair is common for patients with tumors that secrete the b-subunit of human chorionic gonadotropin (hCG). We report a 3-year-old boy with inososexual precocious puberty. The patient presented enlarged testes (5 ml) bilaterally and penis (length 6 cm), pubic hair development of Tanner Stage II. Upon examination, his height SDS was +2.2. Bone age was 3.5 yrs. Hormonal studies showed a prepubertal LH and FSH levels. Serum testosterone level was highly increased (40.7nmol/l). The HCG-secreting tumor was suspected. Ultrasoundography and abdominal CT showed a hepatic tumor, compatible with hepatoblastoma. The diagnosis of HCG-secreting tumor was confirmed by high levels of HCG (179.6 mIU/ml) and alpha fetoprotein (61180 ng/ml). Histopathological examination revealed embryonic and fetal pattern of hepatoblastoma. During repeated hormonal examinations the highest level of 17-hydroxyprogesterone (17-OHP) were found which is not typical for HCG-secreting tumor. The plasma cortisol was at the low limit of normal, plasma DHEAs and androstenedione were normal for chronological age. After 2 courses of chemotherapy and surgery the progression of pubertal signs was stopped, the testosterone, 17-OHP and HCG levels became normal. Thus, the inososexual PP in young children can be the first and the unique symptom of a HCG-secreting hepatoblastoma, which requires its suspicion among others causes of PP.

Twelve cases of juvenile granulosa cell tumors of the ovary: Strategy to improve the therapy

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Background: Juvenile granulosa cell tumors of the ovary (JGCT) account for 5% of pediatric ovarian tumors. They develop from gonadal stroma and sex cords.

Aim: To identify factors important to improve the therapeutic strategy.

Patients: In this monocentric retrospective study (1995 - 2007), the clinical, biological, radiological, histological, molecular, therapeutic data and the outcome of 12 girls treated for JGCT were analysed (mean age at diagnosis: 6 ½ years [range: 0-14 ½], mean follow up: 6 years [range : 3 months-12 years]).

Results: Prepubertal patients (n=9) had endocrine manifestations (hypereosinophilia and hyperandrogenism), whereas the diagnosis was based on an acute abdomen in postpubertal patients (n=3). Signs of virilization were frequent (9/12 cases). A positive correlation was found between the intensity of endocrine signs, the serum hormones levels, the tumor size and the presence of ascites among prepubertal girls. In the present study, no correlation was found between the time from first signs to diagnosis (mean = 5 ½ months, [range : 0,5 - 30]) and the FIGO stage. Inhibin B proved to be a sensitive tumor marker (increased in 6/6 cases). The treatment consisted in an ovaricectomy (n=11) and chemotherapy (n=2) or a tumorectomy (n=1). JGCT showed solid and cystic components (10/12 cases). Immunohistochemistry helped for the diagnosis and provided a prognostic factor (underexpression of FOXL2 in JGCT with aggressive progression). A R 201 C somatic mutation in the gene encoding for the Gαs protein was detected in tumor cells (2/10 cases) and was associated with severity of the disease.

Conclusion: The diagnosis of JGCT must be considered in cases of premenopausal pubertal virilization and/or an ovarian mass with increased inhibin B serum level. This study highlighted that early diagnosis and appropriate surgical treatment, together with chemotherapy in aggressive forms, allowed a favorable outcome. Yet, a prolonged follow up is required.

Prevalence of the metabolic syndrome in adolescent girls with polycystic ovary syndrome is determined by their weight status

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Polycystic ovary syndrome (PCOS) in adult women is associated with increased risk of cardiovascular disease mainly due to insulin resistance and metabolic syndrome (MS). PCOS may be associated with MS also in adolescent girls. The aim of the study was to estimate the prevalence of MS in adolescent girls with PCOS with respect to their weight status. In 34 girls in the mean age 16.5±0.98 years with PCOS diagnosed according to ESHRE/ASRM criteria and in 20 girls in the mean age 16.5±1.2 years with regular menstrual cycles (Control group-CG) BMI, waist circumference and blood pressure were measured. Fasting blood glucose, insulin, lipid profile were tested and oral glucose tolerance test was performed. MS was diagnosed according to modified Cook’s criteria. In PCOS group 13 (36%) patients were obese and 6 (17%) were overweight, compared to 6 (30%) obese and 2 (10%) overweight girls in CG (p<0.05). BMI z-score in girls with PCOS was 0.96±0.83 vs. 0.8±0.96 in CG, the difference being statistically insignificant. MS was diagnosed in 6 (17%) girls with PCOS and in 1 (5%) girl from CG (p<0.05).
All girls from PCOS and CG meeting the criteria of MS were overweight or obese. There was no significant difference between group with PCOS and CG with respect to frequency of MS components occurrence. However high insulin level and increased HOMA-IR appeared more often in girls with PCOS than in CG [18 (50%) vs. 3 (15%), p=0.01; 21 (58%) vs. 4 (20%), p=0.01, respectively]. In PCOS girls MS occurrence correlated significantly with obesity (r=1.0, p<0.001), BMI z-score (r=0.67; p=0.01), fasting hyperinsulinaemia (r=1.0; p=0.002) and HOMA-IR exceeding 2.5 (r=1.0, p=0.01), however no correlation neither with testosterone nor with androstendiene levels was found. It is concluded that MS and its components in adolescent girls with PCOS are determined mainly by obesity and not by hyperandrogenemia.

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Adiponectin and resistin concentrations after glucose load in adolescents with polycystic ovary syndrome: Correlations with risks of cardiovascular disease

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Serum adiponectin and resistin levels in polycystic ovary syndrome (PCOS) has not been as extensively investigated in the adolescent population. Our aims were to evaluate serum adiponectin and resistin levels at fasting and after glucose load and their interaction with risk of insulin resistance index, serum lipids and blood pressure. Twenty-two adolescent girls with PCOS (mean age 15.2±1.1) and age-matched 16 healthy adolescent girls (mean age 15.1±1.1) were included in the study. Girls with PCOS were separated into two groups: ten were obese, which are weight-matched with obese controls, and 12 were normoweight (N-W), which are weight-matched with N-W controls. Hormone samples were obtained from adolescents in between 2nd to 5th days of their menstrual cycle. Fasting serum lipids was measured. Fasting and at 2 hour of OGTT, blood samples for adiponectin and resistin were obtained. Seventeen girls with PCOS (77.2%) had hirsutism and both PCOS groups had similar. Ferriman-Gallway scores of girls with PCOS were higher than the controls. Eighteen girls with PCOS (81.8%) had oligomenorrhea. Seven obese girls with PCOS (70%) had acanthosis nigricans. Fasting serum total cholesterol and LDL-C levels of PCOS group were higher. Adiponectin was lowest in obese PCOS group at fasting and after glucose load while resistin was similar in matched groups. Fasting adiponectin level was positively correlated with ISI (r=0.729, p=0.0001), FGIR (r=0.696, p=0.0001), QUICKI (r=0.592, p=0.004) and HDL-C (r=0.516, p=0.028). Fasting adiponectin was inversely correlated with systolic blood pressure (SBP) (r=-0.711, p=0.0001), waist to hip ratio (WHR) (r=-0.647, p=0.001) and HOMA-IR (r=-0.595, p=0.003). HDL-C was negatively correlated with R (r=-0.713, p=0.001) in PCOS group. We determined significant correlations between in adiponectin and cardiovascular risk criteria such as insulin resistance criteria, SBP, WHR in girls with PCOS.