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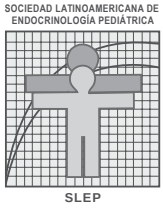
ABSTRACTS



XX Annual Meeting of the Sociedad Latino-Americana de Endocrinología Pediátrica (SLEP)

Lima, Peru, October 11–15, 2008

Guest Editor
Miguel Chávez Pastor, Lima

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Invited Speakers

Prof. Dr. Lydia Aguilar-Bryan	Pacific Northwest Diabetes Research Institute Seattle, WA, USA
Prof. Dr. Jean-Claude Carel	Department of Pediatric Endocrinology Hôpital Robert Debré and Faculté de Médecine René Descartes Paris, France
Prof. Dr. Pinchas Cohen	Mattel Children's Hospital David Geffen School of Medicine University of California at Los Angeles Los Angeles, CA, USA
Prof. Dr. Francis de Zegher	Departments of Pediatrics University Hospital of Brussel, Mont Godinne, Louvain Leuven, Belgium
Prof. Dr. Ieuan A. Hughes	Department of Paediatrics University of Cambridge Cambridge, UK
Prof. Dr. Lourdes Ibañez	Endocrinology Unit Hospital Sant Joan de Déu, University of Barcelona Esplugues, Barcelona, Spain
Prof. Dr. Santiago Muzzo	Unidad de Endocrinología Instituto de Nutrición y Tecnología de los Alimentos Universidad de Chile Santiago, Chile
Prof. Dr. Clifford J. Rosen	Maine Center for Osteoporosis Research and Education St. Joseph Hospital Bangor, ME, USA
Prof. Dr. Jean-Marie Saudubray	Departments of Pediatrics, Radiology, and Surgery Hôpital Necker-Enfants Malades Université René Descartes Paris, France

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Program

Saturday, October 11th

19.30–20.00	Opening Session
20.00–21.00	Opening Lecture **Prof. Dr. Santiago Muzzo** Pediatric Endocrinology in Latin American
21.00	Venue Cocktail

Sunday, October 12th

08.00–08.50	Conference **Dr. Francis de Zegher** Natural history of children small for gestational age (SGA) and normal post natal catch up growth
08.50–10.20	Oral Presentation Session
10.20–10.40	Coffee break
10.40–11.30	Conference **Dr. Pinchas Cohen** Insulin growth factor-based dosing of growth hormone therapy in children
11.30–13.00	Oral Presentation Session
13.00–14.15	Lunch with the Professor **Dr. Francis de Zegher** Origins of PCO **Dr. Lourdes Ibañez** Precocious pubarche
14.30–16.00	ESPE Symposium **Dr. Jean-Claude Carel** Turner syndrome: pubertal management and sexuality **Dr. Ieuan A. Hughes** Androgen receptor gene ligand-binding-domain mutations
16.00–16.20	Coffee break
16.20–17.20	Oral Presentation Session
17.20–18.20	Poster Session
18.20–19.10	Conference **Dr. Pinkas Cohen** Treatment perspectives in idiopathic short stature with a focus on IGF-I deficiency
19.30-20.30	SLEP Business Meeting
21.00	Dinner

Monday, October 13th

08.00–08.50	Conference **Dr. Clifford Rosen** IGF-I in bone and fat: Inter connections for metabolic homeostasis
08.50–10.20	Oral Presentation Session
10.20–10.40	Coffee break
10.40–11.30	Conference **Dr. Jean Marie Saudubray** Genetics of hypoglycemias: A pathological approach
11.30–12.20	Conference **Dr. Lourdes Ibañez** Polycistic ovarian syndrome: Diagnostic and treatment in the adolescent patient
12.30–17.00	Lunch and Outdoor day
18.00–19.30	SLEP Business Meeting
21.00	Dinner

Tuesday, October 14th

08.00–08.50	Conference **Dr. Lydia Aguilar-Bryan** ATP-sensitive K^+ channels: An historical perspective
08.50–10.20	Oral Presentation Session
10.20–10.40	Coffee break
10.40–11.30	Conference **Dr. Clifford Rosen** The Genetics of IGF-I
11.30–12.20	Conference **Dr. Jean-Claude Carel** Management of short stature with GnRH agonist
13.00–14.15	Lunch with the Professor **Dr. Clifford Rosen** Regulatory determinants of IGF-I **Dr. Jean-Claude Carel** Long term safety of GH after childhood treatment
15.00–15.50	César Bergadá Conference **Dr. Ieuan A. Hughes** Consensus statement of management of intersex disorders
15.50–16.50	Oral Presentation Session
16.50–17.50	Posters – Coffee break
17.50–18.40	Conference **Dr. Lydia Aguilar-Bryan** Role of ATP-sensitive K^+ channels in hyperinsulinemic hypoglycemia
18.40–19.30	Conference **Dr. Jean Marie Saudubray** Clinical approach to treatable inborn metabolic diseases: An introduction
19.30–20.00	Closing Ceremony
21.00	Gala Dinner

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Horm Res 2008;70(suppl 2):1–31

Oral Presentations

1

Mild Fasting Hyperglycemia in Children: High Rate of Glucokinase Mutations and Some Risk of Developing Type 1 Diabetes Mellitus

A. Rocha, L. Deng, A. Martínez-Aguayo, V. Mericq, C. Godoy, W. Chung, E. Codner

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Background: Incidental hyperglycemia in children generates concern about the presence of preclinical type 1 diabetes mellitus (T1DM)

Objective: To genetically evaluate MODY2 and MODY3 and the short-term prognosis in children with mild hyperglycemia and a positive family history of diabetes mellitus.

Subjects: Asymptomatic children and adolescents, younger than 15 years, with fasting hyperglycemia, a positive family history of mild non-progressive hyperglycemia and negative pancreatic autoantibodies were studied.

Methods: Glucokinase (GCK) and Hepatocyte Nuclear Factor 1 alpha (HNF1-α) causing Maturity Onset Diabetes of Youth 2 (MODY2) and MODY3, respectively, were sequenced. The clinical outcome was evaluated after a follow-up period of 2.8 ± 1.3 yr (range: 1 to 4.8 yr.)

Results: GCK mutations were present in half of the children. The confirmation of this diagnosis allowed discontinuation of insulin in two families and oral medications in three families. Mutations of HNF1-α were not detected in any of the families.

During the follow-up period, all the GCK mutation carrier children remained asymptomatic without medication and the last fasting blood glucose (BG) and HbA1c levels were 114 ± 13 mg/dl and 6.4 ± 0.7 %, respectively. In the GCK negative children (N = 7), one developed type 1 diabetes mellitus, corresponding to 14.3% of the GCK negative children or to 7.2% of the total group. Mild fasting hyperglycemia persisted during follow-up in four GCK negative children and normalized in the remaining two.

Conclusions: Incidental hyperglycemia in children with a positive family history of diabetes is frequently associated with GCK mutations. The molecular diagnosis allowed discontinuation of medications in several families. However, in those children without a GCK or HNF1-α mutation there is some risk to develop type 1 diabetes mellitus

Sources of support: NIDDK 52431, DERC and ORC DK-04-021

2

Impaired Postreceptor IGF-1 Signaling in Skin Fibroblasts from Children Born Small for Gestational Age (SGA)

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Laboratório de Hormônios e Genética Molecular LIM/42, Disciplina de Endocrinologia da FMUS, São Paulo, Brasil

Introduction: The role of post receptor defects in IGF-1 signaling on the deficit of growth is still unclear.

Objective: To assess IGF-1 action in fibroblasts from SGA children.

Methods: Fibroblast cell cultures were developed from 4 SGA children with clinical IGF-1 insensitivity, defined by severe pre and postnatal growth impairment without any evident cause, IGF1 SDS > 0 and poor growth response during high doses of hGH treatment. Mutations in *GHR*, *IGF1* and *IGF1R* gene were ruled out. IGF-1 action was assessed by cell proliferation. The expression of *IGF1R* gene was determined by Real-time RT-PCR and the levels of the IGF1R protein by direct immunoblotting. IGF-1 signaling was assessed by AKT and ERK phosphorylation after IGF-1 stimulation by immunoblotting.

Results: Fibroblast proliferation induced by IGF-1 was on average 60% lower in 3 SGA cell lines in comparison with the controls. The expression of IGF1R mRNA and the level of total amount of IGF1R protein were similar in all SGA and control cell lines. Despite normal structure, quantity of IGF-1R and similar total AKT and ERK, the same 3 SGA cell lines that presented low proliferation response also had 50 to 85% lower ERK phosphorylation after IGF-1 treatment. All SGA cell cultures presented normal AKT phosphorilation.

Conclusions: The IGF-1 insensitivity observed in these SGA children is caused by abnormal RAS/MAPK pathway, instead of mutations in *IGF1R* gene. This is the first report demonstrating IGF-1 postreceptor signal impairment in children with pre and postnatal growth retardation unresponsive to hGH therapy.

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3

Ghrelin Plasma Levels in Patients with Idiopathic Short Stature (ISS)

V. Mericq, R. Román, M. Hernández, R. Youlton, F. Cassorla, H. Iñiguez

IDIMI, Facultad de Medicina, Universidad de Chile, Departamento de Pediatria, Clinica Las Condes, Santiago, Chile

Novel molecular insights have suggested that Ghrelin, a growth hormone secretagogue and orexigenic hormone, may be involved in the pathogenesis of some forms of short stature. Recently Pantel et al (JCI,2006), described a GHSR missense mutation that segregates with short stature in 2 unrelated families. Our aim was to study Ghrelin plasma levels in prepubertal patients with ISS. Mean Chronological age was 8 ± 0.5 yrs and mean BMI 17.9 ± 0.3 Kg/m2. Fasting total plasma Ghrelin levels were determined by RIA (Linco Research, St. Charles, Missouri) in patients with ISS and compared with age and sex-matched controls with normal height. The sensitivity of the Ghrelin assay was 93 pg/ml, with an Intra CV of 6.5% and inter CV of 12.1%. In a subgroup of 20 patients GHSR was sequenced. Statistical analysis was performed with SPSS 10.0 for Windows. * $p < 0.001$ ** $p < 0.005$ ^$p < 0.05$ ISS patients exhibited a significant higher level of ghrelin (1458 ± 137 vs 935 ± 55**(pg/ml))and a lower level of IGF-I (165.2 ± 11.3 vs 183.5 ± 6.9^ ng/ml) compared to controls. Ten patients with ISS had Ghrelin levels greater than 2 SD of controls. These patients did not differ in height SDS, BMI SDS or IGF-I levels when compared to ISS patients with Ghrelin levels within the normal range. Molecular analysis of GHSR did not show mutations but polymorphisms. Performing ANOVA among the groups according to the polymorphism did not show differences in BMI (SDS), Ghrelin and IGF-I (SDS). These results suggest that in some ISS patients, short stature may be caused by abnormalities in Ghrelin signalling.

4

Genetic Diagnosis Allows Successful Transfer from Insulin to Sulfonylureas in Patients with Neonatal Diabetes Mellitus (NDM)

E. Codner, H. García, F. Ugarte, X. Gaete, R. Silva, M. Arriaza, V. Mericq, S. Ellard

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Introduction: DM diagnosed in children younger than 6 months may be caused by heterozygous activating mutations in KCNJ11 or ABBC8, encoding the Kir6.2 and sulfonylurea receptor subunits, respectively of the pancreatic beta cell ATP-sensitive potassium channel.

Aim: To study the molecular etiology of NDM, and the long term outcome in children transferred from insulin to sulfonylurea treatment.

Methods: Children who had NDM were studied (N = 12). The coding sequences and intron-exon boundaries of the KCNJ11, ABCC8, INS and GCK genes were sequentially performed. Those patients with a mutation in KCNJ11 or ABCC8 genes were offered the possibility of transfer to sulfonylureas.

Results: One half of the patients had an identifiable mutation: three of them had an activating heterozygous mutation of KCNJ11 (two patients had a R201H and the remaining a R201L mutation; Pt 1−3), one had a heterozygous missense mutation (Q211K) in the ABCC8 gene (PT4) and two siblings (PT5−6) were compound heterozygotes for the novel missense mutations L438F and M1290V of the ABCC8 gene. Their parents, who were diagnosed with DM2 during their fourth and fifth decade of life, carried one abnormal allele. Successful transfer to glibenclamide was performed in PT1−4. PT5−6 declined to be transferred. The patients who were transferred have been followed for 26 ± 6.2 months with a decrease of HbA1c levels from 8.9 ± 1.8 to 6.2 ± 0.8%.

Conclusions: The molecular diagnosis allowed discontinuing insulin. Treatment with sulfonylureas allowed an optimal metabolic control in a high proportion of patients with NDM.

5

Role of IGF System in the Preservation of Immature Germ Cells (IGC) Pool in Human Testis

E. Berensztein[1], M. Baquedano[1], J. Accorint[1], C. Pepe[1], N. Saraco[1], R. Ponzio[2], M. Rivarola[1], A. Belgorosky[1]

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A complex network of signs is involved in the regulation of IGC pool preservation. The mechanisms that might participate are unknown. We have shown that aromatase (ARO) and beta estrogen receptor are expressed in IGC from prepubertal human testis (HT). We described that ARO expression change with the age, being higher in HT from neonatal (NEO) and postnatal activation (PNA) than during prepuberty (PP) (Berensztein, Ped Res 2006). In this study we analyzed the expression of IGFs system and insulin receptor (IR) as possible target in the IGC pool regulation.

HT (n = 36) were divided in 3 age groups (Gr): Gr1 NEO (< 1 mo), Gr2 PNA (1−7mo), Gr3 PP (early and late PP). Immunoexpression of c-kit (marker of IGC), IGF1, IGF2, type 1 IGF receptor (IGFR) and IR in GC was studied. Data were expressed as % of positive GC, x ± DS.

c-kit expression was significantly higher in Gr1 and Gr2 than in Gr3 (41.7 ± 14.3, 24.4 ± 17.3, 14.5 ± 13.2, $p < 0.05$). Also c-kit expression decreased significantly with the age ($r = -0.458$, $p = 0.021$). High expression of IGF2 (25.6 ± 3.1, 29.2 ± 7.1 and 28.3 ± 9.6) and IR (37.3 ± 11.9, 41.4 ± 11.3 and 50.8 ± 6.5) while moderate expression of IGF1 (9.08 ± 7.89, 6.7 ± 6.97 and 8.81 ± 3.65) and IGFR

(7.75 ± 5.59, 13.0 ± 13.2 and 4.63 ± 7.21, Gr1, Gr2 and Gr3 respectively) were observed.

The decreased in c-kit expression with age, might suggest changes in the GC population in HT during PP. Since the percentage of IGF1, IGF2, IGFR and IR expression in GC do not change in function of age, it can be suggested that IGFs system and insulin might have a role in maintaining an adequate IGC pool in the HPPT.

6

Chronic Administration of Insulin Like Growth Factors (IGFs) Modulates Response to Human Chorionic Gonadotropin (HCG) by Leydig Cells of Human Prepubertal Testes (HPT) In Culture

M. Costanzo[1], *E. Berensztein*[1], *M. Baquedano*[1], *N. Saraco*[1], *R. Domanico*[2], *M. Murano*[2], *M. Rivarola*[1], *A. Belgorosky*[1]

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We have previously published (Berensztein et al, Ped Res 2008) the characterization of the expression of IGF1, IGF2, IGF receptor type 1 (IGFR1) and insulin receptor (IR) in HPT of 3 age groups (GR): GR1, neonates; GR2, postnatal activation; GR3, early prepuberty, as well as the effect of IGF1 on cell proliferation and apoptosis, P450scc expression and testosterone (T) secretion, in primary culture. A role for IGFs in the modulation of Leydig cell differentiation was proposed. In this study, we have analyzed the effect of chronic stimulation by IGF1 on hCG acute response. HPTs, collected at necropsy, were grouped for culture, as published. Pre-incubation with IGF1 significantly increased T response to acute hCG stimulation (396 ± 133 % of basal; mean ± MSE; $n = 7$; $p < 0.05$). Moreover, in one culture of GR1, IGF2 significantly increased T secretion (175%, $p < 0.05$) in the absence of other stimuli, real time RT-PCR of type 2 3beta-hydroxysteroid-dehydrogenase and 17alpha-hydroxylase enzymes on day 6 of culture (5.7 and 8.2 times respectively; 2-deltadeltaCT), and T response to acute hCG stimulation (237 %, $p < 0.05$). This last effect was blocked by the presence of picropodophyllin, a selective inhibitor of IGFR1. These results are in favor of the hypothesis that the IGF system modulates functional differentiation of Leydig cells, in HPT.

7

Kinetics of the Nuclear Translocation of STAT5b in Immortalized Normal Control Lymphocytes, as Studied by Immunocytochemistry. Sexual Dimorphism of the Growth Hormone Receptor Signalling Pathway Response to rhGH

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Growth retardation and low concentrations of IGF-1 with normal or increased serum growth hormone GH define GH insensitivity (GHI). Delay in nuclear translocation (NT) could indicate insensitivity, as demonstrated in generalized glucocorticoid resistance. Kinetics of NT of transcription factors in the GH signalling pathway has not been previously described. The kinetics of GH-induced NT of Stat5b, assessed by immunocytochemistry, was studied in normal control lymphocytes of healthy young adults ($n = 13$; 5 men, 8 women). Lymphocytes (immortalized with Epstein-Barr viruses) were stimulated with 500 ng/ml rhGH, in triplicate, for times 0(T0), T15, T30, T45 and T60 minutes. After fixation with formaldehyde-acetic acid, immunocytochemistry was carried out with mouse anti Stat5b as primary antibody, and CSA K1500 (DAKO). Marked nuclei were counted, and results were expressed as fold increment of percentages of positive nuclei respect to basal. Mean ± SD for each study time was as follows: T15:1.9 ± 0.6, T30:2.4 ± 0.5, T45:1.8 ± 0.4 and T60:1.4 ± 0.4, all different from basal values ($p < 0.0001$). T30 is the usual maximum peak time of nuclear localization after rhGH stimulation. A sex difference was found in the area under this peak (fold X minutes), men 60.7 ± 15.1 vs women 35.0 ± 8.4, ($p < 0.006$). We conclude that induction of NT of Stat5b, assessed by immunocytochemistry, could be a useful test to study alterations of the GH receptor signalling pathway. Our preliminary data show a sexual dimorphism of the GH receptor signalling pathway response to rhGH.

8

Reduced STAT3 Nuclear Translocation in Fibroblasts from Children with Short Stature and Apparent Growth Hormone Insensitivity

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Introduction: The STAT proteins play an important role in GH signal transduction. STAT5 proteins have been studied extensively in children with short stature, but there is scarce information available regarding STAT3.

Table for Abstract 8

		Arbitrary Units					Area Under Curve		
Height (SDS)		total nuclear STAT3			cytoplasmic pSTAT3		nuclear STAT3	cytoplasmic	pSTAT3 N/C
t'		15	30	60	15	60			
C	−0.2±0.2	0.7±0.05	0.7±0.05	0.7±0.05	0.8±0.04	0.7±0.04	43.±2.8	87.8±2.7	68.2±4.9
P	−2.6±0.2	0.6±0.04*	0.6±0.04*	0.6±0.04*	0.8±0.04	0.9±0.05*	34.1±2.1*	99.1± 4.6*	52.2±4.3*

*p<0,05

Objective: To study total and phosphorylated STAT3 after GH stimulation in fibroblasts from children with short stature and apparent GH insensitivity and control children of normal stature.

Methods: We studied 21 prepubertal children with a mean age of 9.2 ± 0.7 years, short stature (height −2.6 ± 0.2 SDS), decreased growth velocity (< p10), a GH response > 10 ng/mL to two stimulation tests and decreased serum IGF-I/IGFBP3 levels (< −1 SDS), and 31 control children of normal stature with a mean age of 6.1 ± 0.6 years. In fibroblast cultures obtained from a skin biopsy, stimulated with GH at a concentration of 200 ng/ml (15, 30 and 60 minutes), the levels of total and phosphorylated STAT3 were analyzed in the cytoplasmic and nuclear fractions.

Results:

See table above.

In our group of short patients with apparent GH insensitivity, we observed a reduction in total nuclear STAT3 levels, an increase in phosphorylated citoplasmatic STAT3, and a lower nuclear/cytoplasmatic STAT3 phosphorylated ratio compared to the control children.

Conclusion: These results suggest that some children with short stature and apparent GH insensitivity exhibit a reduction in the nuclear translocation of their total and phosphorylated STAT3, which may be related to their growth retardation.

9

Two Novel Mutations (p.G6R and p.R510W) in IGF1R Gene in Children Born Small for Gestational Age (SGA) Without Catch-Up Growth

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Background: Recently, IGF-1 insensitivity caused by IGF1R mutations was identified in children born SGA.

Objectives: Describe two novel IGF1R mutations.

Patients and methods: Twenty-five children born SGA without postnatal catch-up growth who present IGF-1 SDS levels above mean were selected. Peripheral blood leukocytes were isolated followed by total RNA extraction and cDNA synthesis. The IGF1R cDNA was amplified using specific primers followed by direct sequencing.

Results: Two nonconservative missense mutations in IGF1R were identified in 25 SGA children (8%) in heterozygous state: a nucleotide substitution (G > A) at the first nucleotide of codon 6 (exon 1) replacing glycine by arginine (p.G6R) and a nucleotide substitution (C > T) at the first nucleotide of codon 510 (exon 7) replacing arginine by tryptophan (p.R510W). G6 residue is located in signal peptide region of pro-IGF-1R, whereas R510 residue located near of the first disulfide bond between the two alfa-subunits of the IGF-1R protein at cysteine 543. Both affected children were born SGA after an uneventful pregnancy (born weight SDS = -2.5) and presented poor postnatal growth: height SDS −3.3 and −2.3 at 7.4 and 5.8 years of age for children with G6R and R510W mutations, respectively. Patient carrying R510W has microcephaly. Both patients presented normal basal and stimulated GH levels, whereas IGF-1 SDS levels in the upper normal limit.

Conclusion: Two novel mutations (p.G6R and p.R510W) in IGF1R are described, and demonstrate the importance of IGF1R mutations in children with pre and postnatal growth retardation.

10

A Need for Harmonization of Analytical Methodologies in the Newborn Screening for Congenital Adrenal Hiperplasia

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Introduction: The experience with UMELISA 17OHP Neo of TecnoSUMA (TS) in a National Newborn Screening Program in Argentina revealed discrepancies with other methods and the necessity to evaluate its cut off values.

Objectives: To analyze differences with methodology DELFIA and to evaluate their causal factors.

Materials and Methods: a) Linear correlation between TS and DELFIA was made in 312 blood samples in filter paper. b) Samples from an International Quality Program (CDC, Atlanta. USA) for low, medium and high levels of 17OHP were evaluated. c) In order to corroborate the concentration of TS and DELFIA standards as a cause of the discrepancies, they were assayed by ELISA Siemens Enzaplate Neo 17αOHP and HPLC and the results were compared with the content informed by the manufacturers. TS results were corrected

according to HPLC and compared with DELFIA results. An analysis of Bland Altman was made.

Results: TS method shows higher values than DELFIA, with the following linear correlation TS = 33.7589 + 1.4571*DELFIA; r = 0.5007; p < 0.00001. Bias % of the quality controls were for DELFIA: 21.4% (CV% interassay: 14.3%) whereas for TS: 62.4% (CV% interassay: 21.2%). The Recovery (%) of DELFIA and TS standards according to HPLC tests were 100.6% and 55.8%, respectively; coincident to the recoveries obtained by ELISA: 90.1% and 56.3%.

Conclusions: The collected data are consistent with an underestimation in the calibration of the standards. Its adjustment tends to harmonize the differences, but a bias persists in a way which is not imputable to the calibration of the standards.

11

Frequency of Germline Mutations In Pheochromocytoma Associated Familial Syndromes in an Argentine Population

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More than 25% of pheochromocytoma are hereditary. The inherited pheo-associated syndromes are MEN 2 on account of mutations of the ret gene, VHL on account of mutation of the vhl gene and pheochromocytoma-paraganglioma (Pheo-pgl) syndromes caused by mutations of of the SDHB, SDHD and SDHC genes. The aim of this work was to evaluate the frequency of germ-line mutations in the genes coding for the vhl, ret and SDH (B y D) in a sample of 72 Argentine index patients (4−71 y) having the clinical features of pheo associated familial syndromes. The diagnosis was supported by clinical, biochemical (VMA, E, NE and Calcitonin) imaging (I131 MIBG, TAC, RMN, PET) and confirmed at surgery. We have identified 34 MEN 2A 47%, 5 CMTF 6.9%, 12 MEN 2B 16.6%, 12 VHL 16.6%, 2 SDHD 2.7% and 7 SDHB 9.7%. We have been able to find 12 sequence variants in MEN 2, 3 in SDHB, 2 in SDHD and 10 in VHL. The prevalence of the VHL was high in the young population (under 21y, 10/12), in contrast with the adult population that showed the greatest prevalence of MEN 2 (38/50). Remarkably the sequence variant g300-304delCCTCA was present in high frequency in a group of SDHB patients with malignant pheos being this the only correlation genotype-phenotype that we found. This study show the mutations found in an argentine population and contributes to four novel germ-line vhl mutations and two novel germ-line SDHB mutations.

12

Differentiated Thyroid Cancer (DTC): Presentation and Follow Up in Children And Adolescents

P. Papendieck, D. Braslavsky, A. Chiesa, M. Venara, L. Gruñeiro-Papendieck

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DTC is the most frequent endocrine malignancy in childhood.

Presentation and long term follow up vary from that described for adults. To report the clinical findings, treatment and follow-up of pediatric DTC, we analyzed the clinical charts and anatomopathological reports of 41 patients with DTC (8males)(6,2−19,5 years)(35 pubertal) followed up for 0,16 −13,1 years at the Endocrinology Unit between 6/88 and 6/08.

Results: 31 patients consulted with a thyroid mass, 7 had also palpable cervical lymph nodes (CLN) and 10 multinodular goiter. Tumor size by palpation was < 1cm: 2, 1−4cm: 28 and > 4cm: 10. All underwent total thyroidectomy; 3(7,3%) presented recurrent laryngeal nerve paralysis and 8(20%) permanent hypoparathyroidism.17 had CLN involvement, 4 distant LN metastases (MTS) and 4 lung MTS. FNAB (n:35) was diagnostic in 37,1% and suspicious in 40%. Anatomopathological studies revealed 36 papillary and 5 follicular carcinomas, 23 multifocal and 19 with extracapsular extension. All underwent postoperative radioiodine remnant ablation and l-thyroxin suppressive therapy. 6 recurred: 3 regional LN, 1 mediastinal LN, 1 in lung and 1 indeterminate location. At 5 years of follow up (n:20) 70% had no evidence of disease.

In children DTC mainly presented as a palpable single thyroid mass (31/41) had already LN involvement (56%) and was predominantly papilar (36/41) with multifocal location (56%) and pulmonary MTS (12%). FNAB was a useful tool for diagnosis and therapeutic approach allowed eradication of the disease in 70% of patients followed up for 5 years.

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The Influence of the 737/738 IGF-I Polymorphism on Birth Size, Postnatal Growth, Plasma IGF-I and Cardio-Metabolic Risk in Early Adult Life

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Background: subjects born small (SGA) or large for gestational age (LGA) are at higher cardio-metabolic risk in adult life. It is controversial if IGF-I gene polymorphisms, including the microsatellite 737/738 modify this risk by influencing birth size, plasma IGF-I or postnatal growth. OBJECTIVE: to assess the influence of 737/738

IGF-I genotype on prenatal and postnatal growth and cardio-metabolic outcome in early adult life. METHODS: case-control study nested within a cohort of 2063 subjects followed since birth to 25 years old. Subjects: SGA (n = 199), LGA (n = 117) and 398 appropriate for gestational age (AGA). At birth, 9 and 25 years old: anthropometric measurements. At 25 years: Blood pressure (BP), fasting glycemia, insulinemia, HOMA, lipids and plasma IGF-I. 737/738 IGF-I polymorphism was genotyped by PCR-Genescan.

Results: the common alleles with 19 and 20 CA repeats were considered wild types (WT). Homozygosity for variant alleles (VT) was less frequent in AGA than in SGA (p = 0.04) or LGA subjects (p = 0.002). Non-carriers of the WT alleles presented higher probability to born LGA (OR: 3.2; 95% CI: 1.5−6.9) than AGA. 737/738 IGF-I was not associated with symmetrical or asymmetrical birth size, postnatal catch-up in SGA or catch-down in LGA. SGA carrying WT alleles presented lower BP than homozygous for VT (117/70 vs 124/73; p = 0.01). LGA homozygous for WT presented higher BP (120/73 vs 114/67 mmHg; p = 0.05) and lower plasma IGF-I than VT carriers (p = 0.03). 737/738 IGF-I polymorphism had no effect on others phenotypic traits.

Conclusions: Our data originally demonstrate that the 737/738 IGF-I polymorphism is associated with birth size, plasma IGF-I and BP in adult life.

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Hereditary Disease in Patients Younger than 20 Years of Age with "Apparently" Sporadic Pheochromocytoma

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Pheochromocytomas (pheos) are catecholamine secreting tumors. Familial pheos are found more often than traditionally assumed. This may be due to associations to Multiple Endocrine Neoplasia 2, von Hippel Lindau disease, and neurofibromatosis type 1. Mutations of the gene coding for the D, B and C subunits of succinate dehydrogenase (SDHD, SDHB and SDHC) are known. We evaluated 36 patients with pheo younger than 20 y of age to assess the presence of familiar disease. 12/36 were relatives or had clinical features of familial disease. In the remaining 24 patients molecular studies were performed. We identified germ-line mutations in 15 patients (62.5%); 11 (45.8%) had vhl mutations and 4 (16.6%) of SDHB. The clinical outcome was favourable in 17/24 (follow between 1−40 y), without recurrence or metastasis (10 showed mutations of vhl, 1 with SDHB mutations and 6 were negative). 1 patient died (negative) and 5 were unfavourable: 3 with metastases (1 SDHB, 2 negative), 1 with local recurrences (SDHB) and 1 with hemangiomas (vhl). 2 patients were lost to follow up. The high prevalence of mutations found in these young patients, mainly in the vhl gene, underscores the importance of the molecular studies to better characterize this condition in the patients and other family members and may improve the outcome.

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The Influence of Adiponectin Gene (APM1) Polymorphisms on Birth Size and Cardio-Metabolic Risk in Early Adult Life

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Introduction: Adiponectin (APM1) regulates insulin action. Single nucleotide polymorphisms (SNPs) in APM1 gene may modulate adiponectinemia. However, it is not known if APM1 SNPs are associated with pre and postnatal growth and cardio-metabolic risk in adult life.

Objective: to evaluate the influence of APM1 SNPs on fetal and postnatal growth and cardio-metabolic risk.

Subjects and Methods: case-control study nested within a cohort of 2063 subjects followed since birth to 25 years old.

Subjects: SGA (n = 198), LGA (n = 116) and 398 appropriate for gestational age (AGA). At birth and 25 years old: anthropometric assessments. At 25 years: Blood pressure (BP), glycemia, insulinemia, HOMA-IR, lipids and plasma APM1 (RIA). Four APM1 SNPs (c.-11391G > A, c.-11377C > G, c.45T > G and c.276G > T) were genotyped by RT-PCR.

Results: in adult life, adiponectinemia was associated with birth size (SGA vs AGA: 9.1[5] vs 11.2[5] µg/mL; p < 0.001). Homozygosity of the c.-11391A allele was more frequent in LGA than AGA (p = 0.04). Subjects carrying this genotype have increased probability to born LGA than AGA (OR: 4.1; CI 95%: 1.1−16.7; p = 0.03). In LGA subjects the c.-11391A allele was associated with higher adiponectinemia (p = 0.03). Also in LGA group, homozygous carriers of c.276T allele had significant lower insulin (3.4[2.7] vs 7[6.3] µUI/m; p = 0.01) and HOMA-IR (1.5[1.4] vs 0.7[0.6]; p = 0.01). In AGA group: homozygous carriers of the c.-11377G allele had increased diastolic BP (82[7] vs 69[8] mmHg; p = 0.02). Carriers of the c.45G allele had lower DBP (67[4.9] vs 71[9]; p = 0.03). Carriers of the c.276T allele presented higher glycemia (84[9] vs 81[8]; p = 0.008). In the SGA groups APM1 SNPs were not associated with metabolic features.

Conclusion: polymorphisms in APM1 gene may influence prenatal growth and are associated with cardio-metabolic features, including adiponectinemia, in young healthy adults.

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The –202 A Allele of Insulin-Like Growth Factor Binding Protein-3 (IGFBP3) Promoter Polimorphism is Associated with Higher IGFBP-3 Serum Levels and Better Growth Hormone Response to Growth Hormone (GH) Treatment in Patients with Severe GH Deficiency

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Introduction: Genetic factors that influence the response to hGH therapy remain mostly unknown. To date, only growth hormone receptor gene has been investigated. The aim of the present study was to assess the influence of an IGFBP3 promoter region polymorphism (-202 A/C) (rs2854744), previously correlated with circulating levels of this protein, on IGFBP-3 levels and growth response to hGH therapy in children with severe GHD.

Methods: −202 A/C IGFBP3 genotype was assed in 71 children with severe GHD (peak GH levels < 3.3 µg/l at 2 GH provocative tests) who remained prepubertal during the first year of therapy and who have been treated with a mean GH dose of 32µg/kg/d. GHD children were compared according first year of hGH treatment.

Results: Clinical and laboratory data at start of treatment were similar among genotype groups. Despite similar hGH doses, patients homozygous for the A allele presented higher IGFBP-3 SDS levels and higher mean GV in the first year of hGH therapy than patients with AC or CC genotypes (1st year GV: AA = 13.0 ± 2.1 cm/y, AC = 11.4 ± 2.5 cm/y and CC = 10.8 ± 1.9 cm/y; p = 0.028 for AA vs. AC and p = 0.003 for AA vs. CC). The influence of genotype on GV was independent of other clinical variables, as demonstrated by multiple linear regression analyses.

Conclusions: The −202 A allele of IGFBP3 promoter region is associated with increased IGFBP-3 levels and growth velocity during the first year of hGH treatment in prepubertal GHD children.

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Idiopatic GH Neurosecretory Dysfunction (GHNSD): A Possible Cause of GH Deficiency (GHD)

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GHNSD was described by Spiliotis et al in 1984. Since then, this entity was reported in patients after cranial radiation therapy. However, the diagnosis of idiopathic GHNSD has been questioned. We describe 3 prepubertal patients aged 12, 7.8 and 6.3 years with height of −4.2, −3.3 and −4.3 SDS, respectively and delay in bone age from 3 to 5 years. Target height was normal, without a history of constitutional delay. Psychosocial deprivation was excluded. Arginine-clonidine tests showed a maximum GH peak of 10.8, 16.8 and 17.1 ng/ml, and serum IGF1 (SDS) levels were −4.64, −2.3 and −2.8 respectively.

An increase of IGF-1 > 60% in the GH generation tests excluded GH insensitivity. A twelve-hour 20 minutes sampling nocturnal pulsatile GH secretion was performed and compared with normal prepubertal controls (C).

Spontaneous mean ± SD GH levels (ng/ml) were 0.69 ± 0.3, 1.3 ± 0.8 and 1.4 ± 0.8 vs 4.4 ± 1.4 in C. Pulse amplitude were 0.6 ± 0.39, 1.9 ± 2.1 and 3.4 ± 0.37 vs 8.5 ± 4.3 in C. Max GH were 1.21, 4.2 and 4.6 vs 18.2 ± 9.5 in C. All these values were significantly lower than C, while the number of pulses were not.

GH treatment at a mean dose of 0.23 mg/k/wk resulted in growth acceleration at year one from a baseline of 4.1, 4.0, and 3.2 cm/yr, to 10.1, 10.2 and 7.6 cm/yr, respectively.

These data show that idiopatic GHNSD should be considered when other causes of GHD are excluded even without a history of cranial irradiation. The 12-hour spontaneous nocturnal GH sampling is an alternative test to delineate who might benefit from GH treatment.

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Congenital Hyperthyroidism Caused by Mutation in the Transcellular Domain of the Thyrotropin Receptor

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Introduction: The gain-of-function mutations in the TSH receptor(TSHR) have been identified as the molecular basis for congenital and acquired forms of non autoimmune hyperthyroidism. We described a preterm male newborn (32 weeks), appropriate to gestational age. His mother an adolescent (14 years old) was diagnosed with hyperthyroidism when she was 11 years old, antibodies to TSHR (TRAb) were no available. She had irregular adherence to propylthiouracil therapy. The newborn developed hyperthyroidism at 27 days of life and treatment with propylthiouracil was started with good response. He did not attended controls between 6 to 13 months. At month 13 the hyperthyroidism persisted.

Method: Serum TSH, T4L and T3 to the patient and familiar group were measured. TSHR antibodies and thyroid CT-scan were also performed to the patient. Genomic DNA was extracted from peripheral lymphocytes using standard procedures. The entire coding region of exon 10 was amplified from the patient and his mother.

Results: Hyperthyroidism was diagnosed in maternal grandfather (43 years old) and maternal aunt (Age = 6 months). A new mutation in TM1 of the TSHr gene resulting in the substitution of Arginine for Lysine was found. The receptor expression on the cell surface and its sensitivity were normal, but there the basal cAMP was increased, which could explain the phenotype of the mutation.

Conclusion: We report a new mutation in TM1 of TSHR causing a gain of function. Patients harboring the same mutation of the TSHr gene may show wide phenotypic variability as congenital and acquired hyperthyroidism.

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Twins at Risk: A False Negative Screening Result for Congenital Hypothyroidism

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Among the many published studies of neonatal hypothyroisdism screening, it is surprising to find but a few reports of false negative results. The majority of hypothyroid mono or dizygotic twin pairs, found to have hypothyroidism on screening have been discordant for the disease. We present a female patient who was diagnosed at 49 days of age with the classic signs of severe hypothyroidism, who had a neonatal TSH level of 5 mIU/ml. She was the second of a same-sex presumably monozygotic twin pair. Born at 36 weeks, her birth weight was 2280 g and length 43.5 cm. The first abnormal signs were noticed by the parents at 20 days of age. She was examined by several pediatrician who relied on the normal TSH report and discarded the diagnosis. At 48 postnatal days she was admitted because of an episode of apnea and typical signs of hypothryroidism were found. TSH level was > 75 mIU/ml. Her twin sister had normal TSH levels neonatally and at 50 days. Maternal thyroid autoantibodies were negative. Thyroid gammagraphic scan disclosed an hypoplastic gland. The etiology of this ocurrence might be attributed to an epigenetic phenomenon, an early embryonic somatic mutation or other postzygotic event. The explanation could be admixture of fetal blood between the twins, and protection by the normally functioning thyroid gland of her sister during pregnancy and the first postnatal days. It is now recommended re-testing all twin pairs at 14 days of age; and to reassert pediatricians in their clinical suspicion of hypothyroidism, in spite of an initially normal screening report.

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Insulin Sensitivity in Patients with Turner's Syndrome

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Turner's Syndrome (TS) is associated with decreased insulin sensitivity (IS) and increased risk of Type II Diabetes (DBT). The aim of the present study was to determine the prevalence of impaired of IS in girls with TS in relation to Tanner stage (T), GH therapy and sexual steroid replacement. Fifty three patients were studied. We analyzed body mass index (BMI), glycemia, (G) insulin (I), by ICMA, area under curve (AUC) of G and I with an oral glucose tolerance test (OGTT) and assessed insulin sensitivity by HOMA, QUICKI, G/I index. Patients were divided into groups according T and GH therapy: A1: (n = 8) TI without GH, A2 (n = 10) TII-IV without GH, B1 (n = 17) T I with GH, B2 (n = 6) T II-IV with GH and C (n = 12) TV with previous GH treatment. Groups were compared with prepubertal (PP, n = 46) and pubertal (P, n = 59) controls. No patients had Type II DBT, only one patient with morbid obesity (C) had G intolerance. GH patients (B1 and B2) had lower BMI than patients without GH, (A1, $p = 0.01$ and A2, $p = 0.04$). Prepubertal patients with GH therapy (B1) had higher I and lower G/I index than controls (PP), $p < 0.05$. There were no differences among pubertal patients with and without GH, when compared to controls. BMI had positive correlations with I SDS, QUICKI, HOMA, G/I index and AUC I.

Conclusion: GH therapy induces alteration in IS, in prepubertal girls with TS but this treatment does not increase the degree of insulin resistance normally observed during puberty.

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Usefulness of GnRH Infusion Test in the Diagnosis of Boys with Delayed Puberty

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Differential diagnosis between hypogonadotropic hypogonadism (HH) and constitutional delay of puberty in boys who present with delayed or arrested puberty is controversial.

The aim of this study was to evaluate the usefulness of GnRH infusion test to predict HH in boys with delayed/arrested puberty. Thirty-five boys (10.8−24.8 yr), (30 with absence of and 5 with arrested puberty) were submitted to IV GnRH infusion (0.83 ug/min for 120 min).

LH and FSH (IFMA) were determined at 0, 15, 30, 45, 60 and 120 min. Final diagnosis of complete HH (n = 17) was done with testes < 4 ml at 18 yr, and partial HH (n = 11) when testes enlargement started but remained arrested for at least 1 yr or did not reach 15 ml. ROC curves were used to determine optimal cut-off points.

LH peak occurred between 15 and 120 min, and FSH peak at 120 min. LH peak < 5.8 IU/L showed a 95.8 % positive predictive value (PPV) for HH, with 82% sensitivity (S) and 85% specificity (Sp); the positive likelihood ratio (LR +) was 5.8. FSH peak < 4.6 IU/L showed similar results. Interestingly, basal FSH < 1.15 IU/L had a 100% PPV for HH, (S:64.3%, Sp:100%). Peak LH > 5.8 IU/L and FSH > 4.6 IU/L in the same patient detected constitutional delay of puberty with 85.7% S and 89.2% Sp; LR + was 8.

In conclusion, in a boy with delayed or arrested puberty, a GnRH infusion test is useful to confirm HH when peak of LH and/or FSH < cut off. When both peak values are above cut-off in the same patient, constitutional delay of puberty can be diagnosed with high accuracy. Finally, basal FSH < 1.15 IU/L confirms HH and no further test is necessary.

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Assessment of Testicular Function Using Direct and Indirect Markers of Sertoli Cell in Prepubertal Boys with Bilateral Cryptorchidism

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In childhood, testicular function can be evaluated studying the tubular compartment. The aim of this study was to assess tubular function of bilaterally cryptorchid patients using direct and indirect markers of Sertoli cell function.

We evaluated serum levels of anti-Müllerian Hormone (AMH), inhibin B (InhB) and inhibin subunit Pro-αC by ELISA, and FSH by IFMA in 70 prepubertal boys (5 ± 3.6 years) with bilateral cryptorchidism before surgery.

AMH, InhB and FSH were normal in 13 patients (19%, 4.7 ± 3.3 yr). AMH and InhB were below normal in 42 patients showing primary tubular damage, with elevated FSH in 13 patients (19%, 4.4 ± 3.0 yr) and normal FSH in 29 patients (41%, 5.0 ± 3.6 yr). Within this group, non detectable InhB coexisted with low Pro-αC in 12 cases and with low AMH in 14. Probably, when tubular damage is B expression is affected more readily. Correlation between AMHβsevere, inhibin and InhB was significant (Spearman r 0.73, $P < 0.0001$, $n = 70$), indicating high concordance for tubular assessment. However, AMH was low and InhB was normal in 14 patients (20%, 4.6 ± 3 yr). AMH may detect a testicular damage earlier than inhibin B or may present more false positive results.

Conclusions: Serum InhB and AMH show a significant concordance as tubular damage markers in patients with bilateral cryptorchidism. When tubular damage is severe, the coexistence of non detectable InhB with detectable AMH reflects the different regulation between these two Sertoli cell peptides.

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GHRHR Mutations in Patients with Isolated GH Deficiency (IGHD)

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Introduction: In familial IGHD cases, mutations in the GH release hormone receptor gene (GHRHR) are probably the most common cause. However, in most patients with sporadic IGHD, the molecular etiology is unknown.

Objective: To evaluate the presence of GHRHR mutations in patients with isolated or familial IGHD.

Patients and Methods: Among all GHD patients, we analyzed those presenting severe IGHD (GH peak < 5ng/mL-IFMA), topic posterior pituitary and absence of mutation or gross deletion in GH-1 gene. The entire GHRHR gene coding (13 exons) and boundary regions as well as the proximal promoter (450 bp) were automated sequenced.

Results: Ten patients (9 males), including 4 familial cases (2 families), were studied. Chronological and bone age at diagnosis were 7.8 (4.5) and 4.8 (3.3) years, respectively. All patients presented severe short stature (height SDS: −4.4 [-2.3 to −5.9]) and reduced growth velocity (3.2 [1.6] cm/yr). GH peaks after insulin test (ITT) and L-DOPA were 2 (1.3) and 2.3 (1.6) ng/mL, respectively. Anterior pituitary size was reduced in 7 patients (70%). Growth velocity in the first year of rGH treatment was 10.9 (2.2) cm/yr. Mutations in GHRHR gene were found in the 4 familial cases and in 1 sporadic IGHD patient. In 3 brothers we observed the previously not described compound heterozygous mutation p.[L144H] + [A176V]. One patient with ancestors from the northeast region of Brazil and family history of GHD harbored the c.57 + 1G > A (IVS1 + 1G > A). In a patient with sporadic IGHD the heterozygous p. L144H mutation was observed. Several single nucleotide polymorphisms (SNPs) in coding and intronic regions of the GHRHR gene were found: p.A57T, p.M422T, c.154-10T > C, c.1104 + 20C > T and c.975-26G > A. In the promoter region, the SNPs c.-261C > T e c.-235C > T were observed in 90% and 60% of the patients, respectively. The frequencies of all SNPs were similar among patients and normal subjects. There was no phenotypical difference among patients with or without GHRHR gene mutations.

Conclusion: Mutations in the GHRHR gene are common in familial IGHD and infrequent in sporadic cases.

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New Steroidogenic Factor 1 (SF1) Gene Mutation. An Extreme Phenotypic Variation was Present in Two Siblings with a 46 XY Disorder of Sexual Development (DSD), and Normal Adrenal Function

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A broad phenotypic spectrum of gonadal, adrenal and Müller duct differentiation has been described in 46XY DSD patients with SF1 mutations. However, functional activity of the adult testis remains unknown. We report two siblings with a 46XY DSD with different degree of masculinization and preserved adrenal function. The index case was first seen at 3 month of chronological age (CA) with perineal hypospadias, 2.5 cm phallus and palpable gonads in scrotum. Basal levels (B) of LH (1.1MIU/ml) and FHS (4.6MIU/ml) were within normal range, and testosterone (T) increased to 2.48 ng/ml in response to hCG. Male sex was assigned and currently, at 18 years

old, he presents normal adult male development, testicular volume (TV) of 10 cc, without evidence of müllerian remnants (MR) on ultrasound, B levels of LH, FSH and T within normal range for age and sex, (LH 2.82, FSH 6.48, T 4.3, resp.) and normal adrenal function. The sister was evaluated at 9 month of CA with pronounced undermasculinized genitalia, presence of uterus on ultrasound, and evidence of severe testicular dysgenesis. In both siblings a heterozigous mutation was found in the SF1 gene, W279X. This mutation, not previously described, predicts the lost of a large part of the ligand binding site and the AF2 domain. This is the first case of a 46 XY patient with a SF1 mutation raised as male, with spontaneous male pubertal development, normal levels of T, LH and FSH, and subnormal TV. It is concluded that an extreme phenotypic variability can be observed in siblings with the same mutation.

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Metabolic Syndrome (MS) Traits and Cardiovascular Disease (CVD) Risk Factors in Childhood Medulloblastoma Survivors

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To analyze CVD factors in medulloblastoma survivors. We evaluated 16 survivors, compared to 9 age-, sex- and body mass index (BMI)-matched controls according to clinical, anthropometric and endocrine-metabolic parameters, body composition (electric bioimpedance), common carotid intima-media thickness (IMT) and doppler echocardiogram. MS criteria were analyzed according to National Cholesterol Education Program Adult Treatment Panel III (NCPEP-ATP III) and International Diabetes Federation (IDF), and modified to evaluate children and adolescents. Age at study assessment was 18.0 ± 4.4 and 20.0 ± 5.1 yr for patients and controls, respectively ($p = 0.3062$). While compared to controls, patients showed increased body fat ($p = 0.0928$), waist circumference ($p = 0.0239$), waist to hip ratio ($p = 0.0009$), and waist to height ratio ($p = 0.0059$). Moreover, they exhibited decreased HDL-cholesterol ($p = 0.0528$) and increased total cholesterol to HDL ratio ($p = 0.0914$), increased fasting glucose ($p = 0.0446$) and insulin ($p = 0.0194$), decreased glucose to insulin ratio ($p = 0.0632$), and increased HOMA ($p = 0.0176$), even though they did not illustrate insulin resistance. Carotid IMT showed no differences. However, echocardiografic parameters showed decreased systolic function in patients, but with no clinical relevance. The individual analysis of MS criteria did not show increase in the requirements of MS in patients. In conclusion, medulloblastoma survivors showed increased total fat, visceral adiposity, and adverse lipid profile. These patients should be monitored in order to reduce the risk of premature CVD.

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Molecular, Histological and Long-Term Survival in 38 MEN2A and FMTC Juvenile Carriers with Prophylactic Thyroidectomy

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Multiple endocrine neoplasia type 2 (MEN2) is an inherited disease caused by germline mutations in the RET proto-oncogen. Carriers of RET mutations are at risk for developing medular thyroid carcinoma (MTC) at young age. Detection of mutations of the RET proto-oncogen provides the basis for prophylactic thyroidectomy in children. In the present study, we report the results of prophylactic thyroidectomy in 38 carriers of RET mutations performed at ages from 17m to 21y (median 10y; males:22; females:16). Twenty seven carriers belonged to 15 families with MEN 2A and 11 to 3 families with FMTC. Level 2 mutations were harboured by 38 carriers: 36 in exon 11 codon 634, and 2 in exon 11 codon 611. Histology was normal only in a 4-year-old carrier. The other 37 carriers had C-cell hyperplasia and in 30 of them MTC was present. MTC was unilateral in 13 and bilateral in 17. In 4/17 bilateral, multifocal MTC was found and one of them presented regional lymph node metastases. Preoperative basal calcitonin levels were increased in 16/38 children: in 3/9 younger than 5 y, in 3/15 with ages between 5 and 10 y and in 10/16 of 11 to 21y. In all patients under 10 y calcitonin levels dropped to normal after surgery while they remained high in 3/10 patients older than 10 y. All patients are alive followed up between 1 and 25 y post thyroidectomy. No patient presented any other associated endocrine neoplasia indicating that MTC is the first manifestation of MEN2A in juvenile carriers. The results of this study emphasize the importance of early screening and preventive thyroidectomy in children at risk to develop MTC.

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Genotyping of a Polymorphism in the Promoter Region of IGBP3 Gene Might Improve the Utility of IGFBP-3 Measurement in the Differential Diagnosis of Children with Short Stature

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Variability of IGFBP-3 levels is related to polymorphic variants in the promoter region of IGFBP3 gene.

Aims of this study: to determine this effect in normal (N), idiopathic short stature (ISS), and GHD children and to evaluate if genotyping the IGFBP3 gene may improve the efficiency of IGFBP-3 measurement for the differential diagnosis of short stature.

We enrolled 190 N (4.9−16.6 y), 89 ISS (3.3−17.5 y) and 25 GHD (3.1−17.6 y). IGFBP-3 levels were determined by IRMA, and the −202 A/C SNP by RFLP. Statistical analysis: One-way ANOVA (A) followed by Tukey's and linear trend (LT) tests and ROC curves. IGFBP-3 levels (SDS) were significantly different among −202 IGFBP-3 genotypes, both in N [AA: 0.35 ± 0.17 (mean ± sem), AC: 0.12 ± 0.11, CC: −0.29 ± 0.11; A: $p = 0.0037$; AA > CC, $p < 0.01$; AC > CC, $p < 0.05$; LT: $p = 0.0031$] and ISS children (AA: −0.01 ± 0.30, AC:-0.83 ± 0.15, CC: −1.04 ± 0.21; A: $p = 0.0112$; AA > CC, $p < 0.01$, AA > AC, $p < 0.05$; LT: $p = 0.0032$). In GHD children there was a non-significant trend (AA: −1.82 ± 0.37, AC: −2.08 ± 0.43, CC: −2.73 ± 0.50).

By ROC analysis, with a cut-off levels of −1.68 SDS, the diagnostic efficiency (DE) of IGFBP-3 measurement for GHD diagnosis was 80.7%, sensitivity (Se) 84.3% and specificity (Sp) 68.0%; while using genotype-specific cut-off levels (-1.17, −1.71 and −2.68 SDS for AA, AC, and CC, respectively) DE, Se, and Sp improved to 85.1%, 89.9%, and 68.0% respectively.

This study extends the association of IGFBP-3 levels with −202 IGFBP3 gene polymorphism to ISS, and shows that its determination partially improves the differential diagnosis of short stature.

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Metabolism and Function of High-Density Lipoproteins (HDL) in Children With Metabolic Syndrome (MS)

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It has been suggested that the anti-atherogenic potential of HDL depends on its structure and its antioxidant function. Apolipoproteins and particularly paraoxonase (PON1) seems to play a principal role by inhibition of the inflammatory response contributing to the prevention of the oxidation of the low-density lipoproteins (LDL). METHODS. The subclasses, size and anti-oxidant activity of the HDL were analyzed in 30 obese children with metabolic syndrome (MS) before the age of 14 years and 30 healthy children. The plasmatic HDL were separated on the basis of their size by electrophoresis in poliacrilamide gradient 4−30% in native conditions. The subclasses of lipoproteins were determined by optical densitometry. The anti-oxidant activity of HDL was determined by means of arilestearase activity through the method of Zeller modified by Kitchen. RESULTS. The activity of paraoxonase measured as the concentration of the arilestearase activity was lower in the group of children with MS ($P < 0.05$) Patients with MS has less concentrations of HDL2b ($p < 0.05$). HDL3b and 3c were higher in patient with MS ($p < 0.05$). CONCLUSIONS. In our study we find a lower anti-oxidant activity of HDL in children with MS compared with healthy children. We also find a higher proportion of HDL2b and small HDL in this group. Our findings suggest that probably HDL2b are the involved in the prevention of endothelial disfunction observed in early stages in children with metabolic-syndrome.

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Nocturnal Concentrations of Free T3 (fT3) and Free T4 (fT4) Increase after the Administration of the IGF-I/IGFBP-3 Complex (Iplex) in Small for Gestational Age Prepubertal Children

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Introduction: It is not establish whether IGF-I and/or IGFBP-3 regulates circulating concentrations of thyroids hormones in humans.

Objective: We determined the effect of IGF-I/IGFBP-3 complex over FT3 and FT4 concentrations in small for gestational age children (SGA).

Methods: We studied 15 prepubertal SGA (7F/8M; 7.6 ± 0.5 years). We studied the FT3 (pg/ml) and FT4 (ng/dl) concentrations before and after the sc administration of 1 mg/kg of the IGF-I/-IGFBP-3 complex (Iplex). The samples for measurement of FT3 and FT4 (basal and post Iplex) were obtained at 23:00; 03:00 and 07:00 hrs. We also determined serum IGF-I and IGFBP-3 at 23:00 and 03:00 hrs (post Iplex).

Results: Four hours after Iplex the IGF-I and IGFBP-3 concentrations increased from 225 ± 21 to 469 ± 32 ng/ml and from 2.7 ± 0.2 to 3.3 ± 0.3 mg/L, respectively (mean ± SEM, $p < 0.05$) and as it shows in the table the FT3 and FT4 concentrations increased 8 hours after the Iplex administration compared with the basal condition.

	23:00 hours	03:00 hours	07:00 hours
T3L basal	3.1±0.2	2.9±0.1	2.7±0.2
T3L Iplex	3.0±0.3	2.8±0.2	3.5±0.3*
T4L basal	1.5±0.1	1.5±0.1	1.4±0.1
T4L Iplex	1.6±0.1	1.5±0.1	1.7±0.1*

Conclusion: These findings indicate that the IGF-I/IGFBP-3 complex administration increases FT3 and FT4 concentrations in prepupertal SGA children, suggesting that IGF-I and/or IGFBP-3 may have a positive feed back effect over the secretion and/or synthesis of thyroid hormones in humans.

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Complete GH1 Gene Deletion Detected by Multiplex Ligation Dependent Probe Amplification (MLPA) in Patients with Congenital Growth Hormone Deficiency Type IA

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Introduction: Most patients with congenital isolated growth hormone deficiency (IGHD) type IA have pituitary GH gene (GH1) deletions ranging from 6.7 kb to 45 kb. Southern blot and RFLP have commonly been used for molecular diagnosis. Multiplex Ligation dependent Probe Amplification (MLPA) is a new, high resolution and simple method to detect copy number variation in target genes.

Objective: To validate MLPA as a tool to identify GH1 deletion.

Methods: 4 patients with IGHD type IA with homozygous GH1 deletion (3 patients with 6.7kb deletion and 1 with 7.6 kb deletion) diagnosed by restriction endonuclease analysis were studied by MLPA. This method consists in the sequence-specific probe hybridization to genomic DNA followed by amplification of hybridized probes with fluorescent primers. PCR products were resolved in capillary electrophoresis and analyzed by GeneScan. Salsa MLPA Kit P216 (MRC-Holland), which contains one synthetic control probe and four specific GH1 probes locate at introns 1, exon 3, 4 and 5, were used.

Results: MLPA analysis disclosed GH1 intron 1, exon 3 and exon 4 peaks were completely lost, indicating homozygous deletions of this gene in all patients. However, regarding GH1 exon 5 probe, a 50% reduction of peak height was observed, indicating an unspecific hybridization. MLPA was unable to distinguish patients with GH1 gene deletion of 6.7 kb or 7.6 kb.

Conclusion: MLPA successfully identify GH1 deletion and can be a feasible platform to detect deletion in patients with IGHD type IA.

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Carotid Intima-Media Thickness and Insulin Resistance and Plasma Concentration of IGF-I in Obese Children and Adolescents

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Introduction: Increased carotid intima-media thickness has been recognized as one of the precursors to atherosclerosis. Some studies have shown that insulin resistance leads to an increase in the arterial stiffness as well as an increase in the carotida's thickness. Insulin-like growth factor I (IGF-I) is structurally related to insulin and could be also related to artery thickness' genesis.

Objectives: To compare carotid intima-media thickness to plasma IGF-I levels and also to with insulin resistance in overweight children and adolescents.

Patients and Methods: 174 children and adolescents were evaluated (age 4−18 years, mean 10 ± 3 years), with BMI ≥ 85th percentile (48% male). Subjects were separated into groups according to Tanner pubertal stage. Carotid arteries were assessed by ecoDoppler and their intimal medial caliber and thickness were evaluated by color-flow mapping. Subjects underwent fasting blood analysis for glucose, insulin and IGF-I. A value of $p < 0.05$ was considered statistically significant.

Results: Association between HOMA-IR and carotid thickness

Pubertal status n r R2 p

Tanner stage IV-V 38 0.55 0.03 < 0.05

Association between plasma IGF-I levels and carotid thickness: $p > 0,05$ (data not shown).

Conclusion- There is a positive association between carotid thickness and insulin resistance in latter stages of puberty. However, this study didn't show a positive association between plasma IGF-I levels and carotid thickness.

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Molecular and Biochemical Components of Insulin Resistance in Girls with Hyperandrogenic States

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Background: Previous adult studies report that insulin signaling abnormalities in the muscle of patients with hyperandrogenism can predict glucose intolerance and type 2 diabetes. The aim of the current study was to describe these abnormalities in adolescents.

Methods: We analyzed girls with clinical/biochemical hyperandrogenism. Patients were classified as (1) hyperandrogenic (N = 7) if they had a history of precocious pubarche or hirsutism and biochemical hyperandrogenism, and (2) those with Polycystic Ovary Syndrome (PCOS) (N = 13) according to Rotterdam criteria. Analysis of anthropometric (Body mass index [BMI], Waist circumference [WC]) and laboratory data (fasting insulin, OGTT, lipid profile, blood pressure) were analyzed. Muscle biopsies were obtained from vaste externe and IRS-1, IRS-2. GLUT-4 expression was measured by RT-PCR in vivo and after culture. Biopsies from non-obese non-hyperandrogenic adolescents were used as controls (N = 6).

Results: IRS-1 and IRS-2 expression was significantly different in cases versus controls ($p = 0.01$). HDL-cholesterol was significantly lower in hyperandrogenic compared to PCOS girls ($p = 0.01$). There were no significant differences between both hyperandrogenism groups in the prevalence of insulin resistance indexes and metabolic syndrome.

Conclusions: Overexpression of IRS-1 and IRS-2 was persistently detected in the overall sample of hyperandrogenic girls compared to controls. Impaired insulin action involves posttranslational modification of signaling molecules, most likely including altered phosphorylation of IRS-1 and IRS-2 subs

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Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency: Insulin Resistance in Women with Final Height

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Introduction: Studies on congenital adrenal hyperplasia due to 21-hydroxylase deficiency indicates a higher prevalence of obesity, visceral adiposity, insulin resistance and hyperandrogenism, when compared to reference population.

Objective: evaluate the incidence of insulin resistance and dyslipidemy in post pubertal women with congenital adrenal hyperplasia followed at Pediatrics Outpatients clinicas at UNICAMP.

Material and Methods: weight, stature, blood pressure, insulin, glicemy, cholesterol, LDL, triglicerids and Homa IR.

Results: We evaluated 18 patients. The mean age was 2,81) and the mean height was 156 cm. Salt-wasting were observed ± 19,5 years (in 11 patients. There were no significant difference on final height, type of glucocoticoids used and biochemical values when comparing salt-wasting to those with no lost. The mean BMI was 23,2 Kg/m2, 12 patients with values lower than 25 (66,7%), 5 patients between 25−30 (27,8%) and 1 patient with a BMI higher than 30 (5,5%). Waist circumference was adequate in 15 patients (83,3%) and high in 3 (16,7%). From 15 observed patients, 11 (73%) showed insulin resistance (elevated HOMA IR compared to BMI). Total cholesterol was normal for age in 13 women (72,2%) and high in 5 (27,8%), LDL was adequate in all patients and HDL was low in 4 (22,2%). Triglicerids were normal in 16 (88,9%) and elevated in 2 (11,1%).

Conclusion: Post pubertal patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency seems to have more insulin resistance than reference population studies independent of their BMI.

Miniposters

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Polycystic Ovary Morphology (PCOM) Does not Affect Ovulatory Function in Healthy Postmenarcheal Adolescents

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Aims: To evaluate the frequency of PCOM in healthy adolescents at two and three years after menarche (PM) and its association with ovarian function and body composition.

Methods: We performed a prospective study of 21 healthy adolescents (13.8 ± 0.8 years) with ultrasound(US), body composition (DEXA) and hormonal study (leuprolide test) 2 and 3 years PM. PCOM was diagnosed according to the Rotterdam criteria. All the girls were followed during 6 consecutive months with salivary and urinary samples for measurement of progesterone (PG) and LH, respectively, obtained during the 13,18,23 and 28th days of each cycle.

Results: First and second US showed PCOM in 38.1 and 33.3%, respectively; four and three girls showed disappearance and development of PCOM, respectively. Lower basal FSH (4.3 ± 0.9 vs. 5.5 ± 0.9mUI/ml; p = 0.02) and higher 24hr estradiol levels (253 ± 96 vs.149 ± 43pg/ml; p = 0.01), were exhibited in PCOM + and PCOM- group, respectively. The stim 17OHPG, testosterone levels and body composition were similar in both groups.

	PCOM+(n=8)	PCOM−(n=13)	p
Cycle duration (ays)	31.1±6.3	32.0±7.6	NS
Ovulatory cicles by PG / LH / both (%)	44.4 / 47.2 / 25	37.7 / 44.3 / 27.9	NS

Regression model showed no influence of PCOM over frequency of ovulatory cycles.

Conclusions: Presence of PCOM is a frequent and inconstant finding in healthy adolescents and does not appear to affect ovarian function or body composition. This study suggests that PCOM should be considered a physiological condition during early adolescence. (FONDECYT 1050452)

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Effects of Prenatal and Postnatal Androgen Exposition on Gender Identity and Sexual Orientation in Adult Females with Classical 21-Hydroxylase Deficiency

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Females with classical 21-hydroxylase deficiency (CAH) are exposed to prenatal and postnatal androgen excess, and it has been observed a high frequency of homosexuality and bisexuality. However, it remained controversial which period of androgen exposition is critical for the development of these disorders.

Objective: to correlate the gender identity and sexual orientation in CAH adult females with prenatal and postnatal androgen excess. Casuistic: 16 females with salt wasting (SW), 20 with simple virilizing (SV) and 3 females with SV form reared as males.

Methods: House Tree and Person Test and Bleger's questionnaire were performed. To evaluate the prenatal androgen exposition: it was determined the Prader degree (P) of external genitalia virilization in 38 cases (P2 n = 6, P3 n = 24, P4 n = 7, P5 n = 1 case). To evaluate the postnatal exposition: patients were classified according to hormonal control during growth periods: good-normal (n = 20) and poor-high (n = 29) testosterone levels. SV patients were analyzed according to the diagnosis ages, before and after 2 years.

Results: all patients with good control presented female gender identity despite Prader score and age at diagnosis. Four SV patients with P3, late diagnosis and poor control presented male gender identity and changed to male social sex at adulthood. Homosexual orientation was found in 2 SW (P3 and good control) and in 4 SV patients (P3 and bad control). Three SV patients assigned as males presented gender and sexual orientation adequate to male sex. None of patients with P4 and P5 presented disorder of gender identity or sexual orientation.

Conclusions: prolonged postnatal androgen exposition was the unique factor associated with male gender identity or homosexual sexual orientation in CAH females. In this series, we did not observe an influence of prenatal androgen exposition.

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Menstrual Cycle Abnormalities in Adolescents with Type 1 Diabetes Mellitus Under Intensified Insulin Treatment

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Objective: To evaluate whether patients with DMI treated with intensive insulin treatment have menstrual irregularities and to determine its relationship with metabolic control and insulin doses.

Design: Prospective controlled study.

Method: We studied 57 adolescents with DM1 treated with ≥three daily doses of insulin were recruited, and 56 healthy adolescent school girls (C). Both groups were paired by gynecological age and body mass index (BMI). A prospective record of menses was obtained for 6 consecutive months. The average inter-menstrual period (Av) and variability of cycles determined by the variation coefficient (VC), and we determined the frequency of amenorrhea (> 90 d), oligomenorrhea (> 45 d) and polymenorrhea (< 25 d). The effect of BMI, HbA1c, daily insulin dose on Av and VC were determined by lineal stepwise regression.

	DM1 (N = 57)	C (N = 56)
Age (yr)	15.3 ± 1.8	14.7 ± 1.5
BMI SDS	0.6 ± 0.6	0.7 ± 0.8
Cycle duration (days)	48.4 ± 38.6	32.0 ± 7.0*
Variation coefficient (%)	30.2 ± 19.2	23.7 ± 18.4*
Oligomenorrhea (%)	59.6	19.6*
Amenorrhea (%)	12.1	1.7*

*p < 0.05

Results: DM1 adolescents showed a higher Av, VC and prevalence of oligomenorrhea and amenorrhea (Table). HbA1c (B = 5.3; P < 0.001) was the only determining factor on Av and that the daily insulin dose (B = 12.5; p = 0.04) was the only determining factor on VC and DM1.

Conclusion: Adolescents with DM1, even under intensified insulin treatment, show a higher frequency of menstrual irregularities. The abnormalities in the menses are related to higher insulin doses and deteriorating metabolic control (FONDECYT 1050452)

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Clinical Biochemical and Molecular Characterization of Six Pediatric Patients with Thyoid Hormone Resistance (THR)

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Introduction: THR is a disorder characterized by elevated serum levels of thyroid hormones, normal or slightly increased TSH levels that respond to TRH and goiter without clinical hyperthyroidism.

Objective: To describe the clinical, biochemical and molecular findings of 6 children with THR aged 0.52 to 12.7 years from 5 non related families.

Results: patients consulted for hyperthyroidism treated with antythyroid drugs (2), goiter(2), TSH resistance to LT4 treatment (1) and familiar screening for THR(1) 4/5 had goiter, 3/6 taquicardia and 3/5 atention déficit disorder. Diagnostic hormone levels Median (range) were T4 20 ug/dl (12.9−24.4); FreeT4 3.3 ng/dl (2.4−5.6); T3 319 ng/dl (222−425) Basal TSH 2.8 mUI/l(1−15.2) and after TRH administration 7.6 to > 100 mUI/l. Administration of T3 200ug /m2 didn`t supress neither basal nor post TRH/TSH levels. SHbg levels showed a paradoxical decrease (3) or a slight increment (3). 2 had thyroid autoimmunity. During T3 test 3 patients remained asymptomatic, 2 showed an increase of heart rate, body temperature an emotional lability and in one the test had to be stopped because of overt hyperthyroidism. Molecular approach identified in all patients and 3 affected parents single point mutations in exons 9 and 10 of the TRbeta gene always in the T3 binding domain: Exon9: pM313 T, pL341P, pL346F, pN331D, Exón 10: pP453L

Conclusion: THR has a distinctive biochemichal profile with clinical discordance and high variability. Its recognition and molecular diagnosis avoids misleading diagnosis and iatrogenic treatment.

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Androgen Receptor CAG/GGC Repeats in Prepubertal Girls with Hypertricosis

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The transactivation domain of the androgen receptor(AR) includes 2 polymorphic aminoacid repeats. The number of CAG repeats(codes gln) appear to be inversely related to AR function. In the case of GGC (codes gly), numbers other than 23GGC exhibit lower transactivation in response to androgens, suggesting that gly lengths other than 23 may be related to AR function. Our aim was to quantify the number of CAG/GGC repeats in the AR gene of prepubertal girls with hypertrychosis matched to normal control girls.

Methods: We recruited healthy hypertrichotic(n = 42) and control(n = 29) girls. DNA obtained from leukocytes was amplified by PCR with specific primers for the region in exon 1 which contains the GGC or CAG repeats. The number of repeats was calculated based upon the size of the fluorescent amplicons by capilar denaturating electrophoresis.

Results: Hypertrycosis score was16 ± 3 in hypertrichotic vs 3 ± 2 in control girls. The proportion of each GAG(17 ± 3 vs 17 ± 3) or GGC androgen repeats(17 ± 1 vs 17 ± 0) were not statistically different in cases and controls. The combined analysis of CAG/GGC, however, showed a significantly higher prevalence of the most androgen-sensitive combinations(< 18CAG + 17/17GGC and < 14CAG + 17/18GGC) in the girls with hypertrychosis (36% vs 14%, P = 0,042, Mann-Whitney test) compared to controls.

Conclusions: Hypertrichotic girls may exhibit AR(s) with enhanced sensitivity, facilitating the growth of their body hair. The association of GGC17 + CAG < 18 repeats in some girls with hypertrychosis may increase the sensitivity of their AR(s).

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Prevalence and Prognosis of Euthyroid Sick Syndrome (ESS) in Pediatrics

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Introduction: ESS is a transitory variety of thyroid alterations in patients with no thyroid pathologies. It is in discussion if it constitutes a favorable response to stress, or is only a marker of severity of the underlying disease. There is no consensus if it needs treatment. In spite of its high prevalence in adults, in children its prevalence and prognosis is unknown.

Objectives: To establish the prevalence of ESS in critically ill pediatric patients and its association with prognosis of these patients.

Materials and Method: Prospective, analytical, multicenter study in patients from ICU of HEGC and CD which needed invasive mechanical ventilation(IMV) for more than 24 hrs. Excluded: previous thyroid pathology, use of medication that interfered with thyroid metabolism. TSH, freeT4, T3 and reverseT3(rT3) were measured and PRISM score (Pediatric Risk of Mortality) was calculated. Patients were classified according to their mortality risk in low(< 5%), moderate (5−15%) and high(> 15%). Days in ICU, IMV and use of vasoactived drugs(VAD) were registrated.

Results: n = 67;61%males; median age:2,1y(0,1−15). 71% presented ESS. From these, 67% were ESS type I(lowT3; N fT4; N or low TSH; high rT3). 27% were ESS II(lowT3; low fT4; lowTSH; high rT3). 4% with all hormones low. There were no differences in the prevalence of ESS in relation to PRISM. Patients with and without ESS had similar days in ICU, of IMV and use of VAD.

Conclusions and Discussion: ESS is very frequent in pediatrics. In this study, different to what is seen in adults, SEE had no relation with a higher risk of mortality, days in ICU, IMV or VAD.

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Role of Intravenous Desmopressin Test in Etiological Diagnosis of Congenital Nephrogenic Diabetes Insipidus

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Introduction: Congenital nephrogenic diabetes insipidus (CNDI) is a disease of autossomal or X-linked inheritance trait caused by mutations of antidiuretic hormone (ADH) V2 receptor gene or of aquaporin-2 gene, respectively. The interaction of intravenous (IV) desmopressin (synthetic analogous of ADH) with V2 endothelial receptors stimulates the secretion of von Willebrand factor (VWF). The VWF may be quantitatively evaluated by ristocetin cofactor activity (RCA).

Objective: Evaluation of the RCA after desmopressin in two infant boys with CNDI.

Patients and methods: Infant1, 14months-old, presented with fever of unknown origin, failure to thrive, polyuria, hypernatremia(151mEq/L), high plasma osmolality(330mOsm/kg) and hyposthenuria(259mOsm/kg); Infant2, 12months-old, presented with vomits, failure to thrive, polyuria, hypernatremia(156mEq/L), high plasma osmolality(309mOsm/kg) and hyposthenuria(160mOsm/kg). Both were insuccessfully treated with intranasal desmopressin, while hydrochlorothiazide(3mg/kg/day) normalized their natremia and improved their weight gain. They were stimulated with IV g/kg) diluted in SF(50mL) and infused in 30' and RCA wasμdesmopressin(0.3 evaluated at the times 0' and 60'.

Results: In both patients the RCA increased after the stimulus with IV desmopressin (patient1: from 170 to 232%; patient2: from 98 to 136%).

Conclusion: The increase of RCA after IV desmopressin in these patients with CNDI indicates that the function of V2 ADH receptor is normal, suggesting that their disease was caused by mutations of aquaporin-2 gene.

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Diferential Diagnosis of Poliuria and Polidipsia: Clinical and Laboratory Variations of the Water Deprivation Test (WDT) in Pediatrics

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Diagnosis of Central Diabetes Insipidus (CDI) is based on clinical and laboratory studies. Although the WDT is generally used for a definite diagnosis, scarce information exists in children regarding its clinical and laboratory findings. To clarify these issues we studied 31 children (aged 7.25 ± 5.0 years) that underwent a WDT to rule out CDI Weight and urine output were measured hourly. Initial and final plasma and urinary osmolality (freezing point), and plasma ADH (extracted RIA) were measured. Final plasma ADH was plotted on a nomogram related to serum osmolality in a normal population.

The positive predictive value of a final U/P Osm ratio(f U/POsm) ≤ 1.5 towards an inadequate final plasma ADH was 95%, and the negative predictive value of 72%, with a diagnostic efficiency of 83%. So, patients were grouped according to the f U/POsm in: Group A (n = 20) ratio < 1.5, and B (n = 11) > 1.5. Patients from group A had a significant decrement of weight ($p < 0.05$) and higher urine output ($p < 0.006$) than group B. Increment of pADH after the test was significantly lower in group A (0.24 ± 1 pg/ml) vs group B (2.47 ± 2.8 pg/ml), $p = 0.015$.

In summary, a decrement in body weight as well as the urine output during this test are useful information to define pediatric patients with a real incapacity to concentrate the urine. Moreover, the measuring of plasma ADH enabled us to establish that a cut-off f U/P Osm ratio ≤ 1.5 is likely associated with inadequate plasma ADH secretion, resulting in the best tool for the differential diagnosis in children with polyuria and polydipsia.

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Secular Change of Puberal Development in Chilean Schoolage: More Duration and Sexual Dymorphism in Stature

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Background: In Chile obesity quadrupled between 1985 and 2000.

To study Aims: To study changes in puberty of school-agedur-ing this period and its relationship with height and weight variations Material and Methods: In two of the Metropolitan Region school-ages, collected between 1985 and 1987 years (m-1986) and another between the 2000 and 2002 years (m-2001), were selected girls between 7 and 15 years (1820 and 935, respectively) and boys between 9 and 15 years (1504 and 774 respectively). The weight, height and BMI were assessed. The breast (B) in girls and genital (G) development in men, were classified according Tanner (T) stage.

Results: There was an association ($p < 0.0001$)between puberty degree and generation In both sexes. The m-2001 has a lower average age of start puberty than m-1986 (10.6 ± 1.3 and 10.1 ± 1.1 in female and 13.1 ± 1.1 and 12.3 ± 0.8 years in male, respectively) without differences in T 4 and 5. BMI was higher in the m-2001 in both sexes. The m-2001 males, are higher at all Tanner stages; however, m-2001 females have a smaller stature in B2 and B3, without differences in B4 and B5 with m-1986 females.

Conclusion: There is a trend towards earlier start puberty associated with a greater time of puberty and body weight in both sexes. The highest stature in m-2001 males only, gives an account of a sexual dimorphism that could be explained by the greater "mixing" of Chilean women.

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Differences in the Intracellular Signal Transduction Components For IGF-IR in Human Term Placentas from Small, Adequate and Large for Gestational Age New Borns

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Introduction: IGF-I and its receptor (IGF-IR) participate in both pre and postnatal growth. The human placenta expresses the mRNA and the protein for IGF-I and IGF-IR and their intracellular signal components (IRS-1, ERK y AKT).

Objective: To Study the protein contents of IGF-IR, IRS-1, ERK y AKT in human full term placentas from SGA, AGA and LGA newborns.

Methods: We collected 16 SGA, 16 AGA and 16 LGA placentas. We determined the protein contents by Western blot in the fetal and maternal side of the placentas. Results are shown in the table as mean ± SEM: The differences were studied by ANOVA.

		SGA	AGA	LGA
IGF-IR	Fetal	0,2±0,03	0,19±0,03	0,21±0,04
	Maternal	0,19±0,03	0,16±0,03	0,19±0,03
IRS-1	Fetal	0,33±0,03	0,23±0,04[&]	0,46±0,08
	Maternal	0,38±0,04	0,28±0,05	0,46±0,07
ERK 42	Fetal	0,39±0,03*	0,24±0,02	0,30±0,04
	Maternal	0,42±0,04*	0,26±0,03	0,30±0,03
ERK 44	Fetal	0,56±0,05#	0,43±0,006	0,42±0,04
	Maternal	0,59±0,05[#]	0,46±0,05	0,41±0,03
AKT	Fetal	0,54±0,06	0,77±0,09[®]	0,51±0,06
	Maternal	0,51±0,06	0,78±0,06[®]	0,54±0,07

ANOVA $p < 0,05$

*SGA vs AGA and LGA; [&]AGA vs LGA; [#]SGA vs LGA; [®]AGA vs SGA and LGA

Conclusion: The higher contents of IRS-I in LGA placentas and the ERK42/44 in SGA placentas suggest that these IGF-IR signal transduction proteins may influence fetal growth. (FONDECYT 1061082)

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Mutations G183S in 5α-Reductase Deficiency Type II in Patients from Bahia/ Brasil and their Association with Ancestry Markers (Alu): Is a Mutation Responsible for Founders Effects?

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Introductions: The enzyme steroid 5-α–reductase type 2 is the responsible for conversion of testosterone to dihydrotestosterone, which is one of the keys steps during the embryonic differentiation of the external males genitals. Mutations and deletions in 5-α-reductase type 2 gene (SRD5A2) were attributable to an almost complete lack of this enzyme activity. A single base substitution of adenine (AGT) for guanine (GGT) at exon 3 resulted in a serine replacement of glycine at amino acid 183 (G183S). These mutations were previously detected in Brazilian patients from mixed African-European ancestry and in the Dominican Republic. In this study, we check the association of mutations G183S with ancestry markers Alu to determinate the possible existence of founder gene effect.

Methods: Six affected subjects were studied. Theirs DNA were amplified for PCR-multiplex. Thirty one Alu-insertion polymorphisms were used because they are neutral genetic markers of identical descent and present high frequency diversity between European, African and Amerindians populations.

Results: Analysis of Alu-insertion polymorphism revealed a African, Amerindians and Europeans contribution of 33,41%, 38% and 28,78%, respectively.

Conclusions: The results demonstrated that the African, Amerindians and Europeans contribution for mutations G183S are relativity similar. The mutations could be origins in any tree parents populations Studies with news polymorphisms are been carried out to confirm or not the possibly common ancestry of gen.

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Usefulness of the Waist Circumference and Waist/Height Ratio in Infants for Metabolic Risk Assessment

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Introduction: The abdominal obesity is linked to an increased incidence of Metabolic Syndrome and DM2 in youth and adults, and the incidence of premature deaths. The WHO recommends the use of BMI as a diagnostic tool for obesity, simple but nonspecific in the diagnosis of cardiovascular risk factors and fatty tissue location.

Aim: Using waist circumference (WC) and the Waist/Height ratio W/H- r) as a method of screening in healthy school population, in

order to define our cut off point and normal values and compare them with U.S. standards (NHANES).

Material and Methods: A cross sectional analysis in 1147 boys and 1254 girls in ages between 2 to 19 years, in 3 socioeconomic class, including anthropometric measurements for data by sex and age.

Results: 1) The WC increases with age but with a less gain compared with the NHANES group, 2) In late adolescence there is a stable trend in WC, 3) The W/H – r tends to decline gradually with age in men, between girls 12 to 19 years no significant changes were noted. 4) The W/H -r with values greater than 0.53 to 0.54 differ significantly from the NHANES findings where there is increased at the end of adolescence ($p < 0.01$), suggesting a lower frequency of abdominal obesity in our population, 5) There is a lower percentage of children with WC above the 90 percentile American unlike American children ($p < 0.05$). 6) Values greater than 0.54 are outside the normal range and 7) The difference percentile for our group of children against the U.S. was significant different ($p < 0.001$).

Conclusions: To our knowledge this is the first study conducted in our country to determine normal values for these variables, founding significant differences compared to American studies.

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Effect of GH Replacement on Lipid Profile, CRP-hs and the Carotid Intima-Media Thickness (IMT) in Children and Adolescents with GH Deficiency (GHD)

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GHD is associated with unfavorable lipid profile and precocious atherogenic process. Low levels of IGF-1 are associated with the carotid IMT and dyslipidemia.

Aim: to evaluate the effect of GH replacement on the lipid profile, CRP-hs and the carotid IMT in children and adolescents with certain GHD.

Methods: this interventional study evaluated the lipid profile and the IMT of 7 patients (mean age13.7 ± 4.8 yr.), before and six months after the onset of GH treatment. The clinical and laboratory evaluation included weight and height (SD), BMI, total cholesterol, (TC), HDL, LDL, triglycerides (TG), non-HDL cholesterol (nHDL-C), the TG/HDL ratio and IGF-1. The IMT evaluation was performed by two blinded observers ($r = 0.90$, $p < 0.0\ 01$). The median was used for pre and post intervention comparisons (Wilcoxon test, $p < 0.05$). Associations were analyzed by the Spearman correlation test.

Results: After 6 months of treatment, there was a tendency towards reduction of TC (203.5 mg/dl vs. 173mg/dl, $p = 0;12$), LDL (129.2 mg/dl vs. 101 mg/dl, $p = 0.17$), CRP-hs (1.3 mg/L vs. 0.46 mg/L, $p = 0.06$) and IMT (0.46 mm vs. 0.44 mm, $p = 0.13$). No change was noted in other lipid variables. Before treatment, a negative correlation was found between IGF-1 and CRP-hs ($r = -0.82$, $p = 0.08$) and after treatment, between IGF-1 and TC ($r = – 0.94$, $p = 0.03$), LDL ($r = -0.88$, $p = 0.04$) and nHDL-C ($r = – 0.94$, $p = 0.035$).

Conclusion: The correlations observed between IGF-1 and lipid variables and subclinical inflammation suggest that GH deficiency is a prothrombotic state, that can be modified by GH replacement.

Posters

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Relative Bioavailability of Two Drug Products of Somatropin Obtained from the Milk of Transgenic Cows and from Bacterial Culture

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Biohormon® (Bio Sidus S. A., Buenos Aires, Argentina) is the first GH produced in transgenic cloned cows that carry the human GH gene allowing them to express the hormone in their milk. The relative bioavailability of Biohormon® was assessed vs. the reference product HHT®, (somatropin from E. coli, Bio Sidus S. A), upon approval by an independent ethics committee and the National Regulatory Agency (ANMAT). We compared the time-concentration profiles of somatropin in 24 healthy adult volunteers. The study was performed as a randomized, two-period, two-sequence crossover design after inhibition of endogenous GH secretion with lanreotide. After the subcutaneous administration of 1.33 mg of each formulation, somatropin was analyzed. Serum GH was measured by a chemiluminescent assay (ImmuliteNR) and as a marker of biological activity serum IGF-I was assessed by IRMA. Safety was assessed by clinical and laboratory parameters and by the production of antibodies against GH. Pharmacokinetic parameters were analyzed with Winnonlin (Pharsight Corporation, Mountain View, CA, USA). The test/reference ratios of AUC, AUClast and Cmax, were 106.4 (CI90% 100.2−112.9); 105,3 (CI90% 99.1−111.8) and 105.49 (CI90% 92.6−120.1), respectively. No serious adverse events were reported and no GH antibodies were detected. In summary, this study demonstrates that a single dose of Biohormon®, the first somatropin obtained from milk of transgenic mammals, is bioequivalent to the reference product HHT® according to standard criteria of pharmacokinetics.

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Obesity and Associated Cardiovascular Risk Factors in Schoolchildren from Mérida, Venezuela

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Introduction: It was proposed to investigate the frequency of obesity and associated cardiovascular risk factors in schoolchildren of our city, given its influence on the development of atherosclerosis.

Methods: Three hundred and fifty one children, second grade students (10% of the population) of 7.8 ± 0.6 years of age, 47.9% females and 52.1% males, from public and private institutes were studied. Surveys were applied, anthropometric measurements, blood pressure (BP) values and the determination of glucose and lipid profiles, using the system plus LDX (Cholestech) in capillary blood, were taken.

Results: It was observed that 9.7% of subjects had obesity (BMI > pc97) and 14% overweight (BMI pc 90–97). Overweight was more frequent in males (16.9% vs. 10.7%) and obesity in females (13.7% vs 6.0%) ($p < 0.05$). Normal-high BP (pc 90–97) was noted in 38.2% ($p < 0.0001$), dyslipidemia in 64.7% ($p < 0.05$) and metabolic syndrome in 44.1% ($p < 0.0001$) of the obese children, compared to 5.8%, 48.7% and 9% in the normal weight children, respectively.

Conclusion: There is evidence of a high frequency of cardiovascular risk factors associated with obesity among schoolchildren in our city. Strategies for its prevention must be implemented in the population.

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Early Alteration of Glycaemic Regulation in Children with Family History of Metabolic Syndrome

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Introduction: Our aim was to evaluate beta-secretion in insulin-sensitive (IS) and insulin-resistant (IR) children with different fasting plasma glucose (FPG) levels.

Methods: We studied 56 obese patients and 52 siblings (6 – 16 year-old). We registered family history of metabolic syndrome (FH), BMI, waist, FPG, insulin, and calculated HOMA-R and HOMA %B using Matthews's model.

Results: Our HOMA-R cut-off value was 2.5 using ROC curves. IR group showed a proportional increase in HOMA-R and HOMA %B (compensated IR) compared with IS group (IR: 4.2 ± 2.4 and 204.4 ± 126.3% vs IS: 1.4 ± 0.6 and 87.3 ± 42.2%, $p < 0.0001$), with a small increase in glycaemia: 5.4 ± 0.5 vs 5 ± 0.4 mmol/l, $p < 0.01$. On the contrary, in the groups with glycaemia > 5 mmol/l (GII) and > 5.5 mmol/l (GIII), HOMA %B did not change compared with the group with glycaemia < 5 mmol/l (GI) despite of an increment in HOMA-R (uncompensated IR) (GI: 1.86 ± 1.36 and 158 ± 94%, GII: 2.93 ± 2.16 and 148 ± 118%, GIII: 4.0 ± 3.1 and 139 ± 121%; $p < 0.01$ for HOMA-R, $p > 0.05$ for HOMA-%B). This fact was related to a greater frequency of positive FH and a greater frequency of obesity ($p < 0.05$).

Conclusion: a partially insufficient beta-secretion might exist early in obese children with FH of metabolic syndrome when FPG is still normal but greater than 5 mmol/l. These children should be closely followed for early intervention.

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Frasier Syndrome in a Patient with 46XY Testicular Dysgenesis, Nephrotic Syndrome of the Infancy and a IVS9 + 5G > A Mutation in the WT1 Gene

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WT1 gene is involved in early gonadal development, and in both kidney and testicular differentiation. Mutations in the WT1 gene have been described in patients with Denys Drash and Frasier syndromes. Heterozigous mutations of the alternative splicing site located at intron 9 that avoid the synthesis of the WT1-KTS + isoforms are present in Frasier patients. These mutations are characterized by 46 XY sex reversal, testicular dysgenesis with a high risk of developing gonadoblastoma, and late renal failure secondary to focal and segmental glomerulosclerosis. We report a 46XY patient with external female genitalia, abscent gonads on physical exam, and congenital nephrotic syndrome secondary to diffuse mesangial sclerosis, with normal renal function at age 3 y., increased serum FSH for age and sex (22.6 MIU/ml), undetectable AMH and lack of response to hCG. Laparoscopic abdominal surgery revealed a uterus, and intraabdominal dysgenetic gonads with bilateral gonadoblastoma. A heterozigous IVS9 + 5G > A mutation in WT1 gene, previously described in patients with Frasier Síndrome, was found. This patient broadens the phenotypic spectrum of the features previously reported in Frasier Syndrome. These findings suggest that there is no clear differentiation between these two syndromes. The clinical phenotype may depend on the specific tissue regulation in the target organ during embryogenesis.

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Pubertal Characteristic in Healthy Girls Small for Gestational Age (SGA) Compared with Girls Appropriate for Gestational Age (AGA)

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Introduction: There are limited and controversial data concerning puberty characteristics in girls born SGA. The aim of the study was to characterize pubertal course longitudinally in matched healthy girls born either SGA or AGA recruited from the community.

Methods: Inclusion criteria were breast Tanner stage II and a normal BMI. Girls were followed during three years with a complete physical exam, bone age, pelvic ultrasound and gonadal hormones.

Results: Twenty five AGA and fifteen SGA have completed three years of follow up with a similar bone age (12,6 vs 13,1 years(y)), delta bone age (3,1 vs 3,2 y), height (153 ± 0,5 vs 151 ± 0,7cm) and delta height (19 ± 3 vs 17 ± 4cm) in AGA vs SGA respectively (p = NS). 60% of the total group achieved breast Tanner 5 and 38% Tanner 4 at the third year. SGA girls advanced little earlier during the first two years. At the third year 52% of SGA vs 50 % of AGA had Tanner 4 of pubic hair and 32% SGA vs 44 % AGA were in Tanner 5 (p = NS). Ferriman score was not different between groups during the follow up. There were no differences in the ovarian volume and number of follicles between AGA and SGA nor in the age of menarche 12y (AGA) vs 12,4y (SGA). In addition no difference was found when corrected by the maternal age of menarche. Basal levels of gonadotropins, estradiol and androgens were similar in both groups.

Conclusion: After three years of following SGA girls have shown slightly earlier development but not differences in internal genitalia or hormonal levels.

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Absence of Mutations in the Promoter and Coding Regions of STRA8 and NANOS2 Genes in Patients with 46, XX and 46, XY Complete Gonadal Dysgenesis

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Background: In mice fetal gonads, retinoic acid induces meiosis in the female germ cells through Stra8 up regulation, whereas in males, Stra8 is first express in germ cells of adult testes. The embryonic suppression of Stra8 is controlled by a dual mechanism, retinoic acid metabolism Cyp26b1-mediated and Nanos2 expression. It was demonstrated that Nanos2 activate a male-specific genetic program while Stra8 up regulation is one of the earliest manifestations of gonadal feminization during embryogenesis. Our hypothesis is that sex specific signaling retardation caused by mutations in NANOS2 in XY patients or STRA8 in XX patients could disrupt the timing of germ cell fate and consequently induce to gonadal dysgenesis.

Objective: To investigate the presence of mutations in NANOS2 in 46, XY patients or STRA8 in 46, XX patients, both with gonadal dysgenesis.

Patients: 46, XX patients (15 subjects, 5 of them familial) without mutations in the coding region of FSHR and 46, XY patients (20 subjects) without mutations in SRY gene.

Methods: Genomic DNA was extracted from the patients and the exons and proximal promoter of STRA8 or NANOS2 were amplified and sequenced.

Results: A previously described polymorphism was identified in exon 2 of STRA8 (200 G > A) in 8 patients in homozygous state and in 3 patients in heterozygous state; no mutations were identified in the coding or proximal promoter regions of STRA8 and NANOS2.

Conclusions: Mutations in STRA8 and NANOS2 are not the cause of abnormal gonadal development in these cohorts of 46, XX and 46, XY patients with gonadal dysgenesis.

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Terminal 15q26.1-qter Deletion Involving Monosomy of the IGF Receptor 1 (IGF1-R) in Two Boys with Severe Growth Retardation and Dysmorphic Features

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Introduction: The IGF1R(15q26.3) mediates IGFs action. Deletion 15qter encompassing IGF1R gene are associated with intrauterine and postnatal growth failure, microcephaly and mental retardation.

Methods: High resolution karyotype and FISH were performed to delineate the extent of del(15qter) in two patients with growth retardation. The effect of rhGH treatment was evaluated in one of them.

P1: A 9.6 yr-old boy. Height: 115 cm, −3.16 SDS. Physical exam: microcephaly, frontal bossing, cryptorquidia, clinodactylia. Mental retardation.

P2: A 5 m-old boy. At birth: W: 2500g, −1.8SDS; H:41 cm, −5.3 SDS. At physical exam: W: 4750g, −3.46 SDS; H: 53 cm, −5.56 SDS; OFC: 38.5 cm Pc < 3. Triangular facies, low-set ears, small hands and feet, clinodactyly, cryptorquidia, hypoplastic kidneys. Developmental delay. IGF1: 59ng/ml Pc50; IGFBP3: 2.30 mcg/ml Pc50. At 11 m of age the GH peak in response to arginine test was 5.3 ng/ml and GH therapy was started. At 6 yr-old showed SDS gain of H: 96.4 cm, −2.61 SDS; IGF1:240 ng/ml, + 2.0 SDS and IGFBP3:3.88 mcg/ml + 2.0 SDS. Family members showed short stature and MR.

Results: P1 showed mosaicism of ring 15 chromosome 46, XY, r(15)(p11q26)/ 46, XY, dic r(15)(p11q26p11q26)/ 47, XY, r(15)(p11q26)x2.

Paternal's karyotypes were normal.

P2: showed del(15qter) and dup(4qter) inherited from his father carrier of reciprocal translocation: 46, XY, der(15)t(4;15)(q32; q26.1)

Conclusion: Both patients resulted in monosomy 15q26.1-qter with loss of one copy IGF1R and haploinsufficiency of genes related with the stature and dysmorphic features. The rhGH was effective in improving SDS resulting in a better growth response and treatment was continued.

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Central Hypothyroidism (CH) in Patients with Prader Willi Syndrome (PWS) during the First 2 Years (Y) of Postnatal Life

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PWS is a genetic disorder with a well characterized phenotype, including hypothalamic dysfunction and intellectual deficiency. Features during the first 2 years (y) of life are general muscular hypotonia, feeding difficulties, and delay psychomotor development. Endocrine disorders such as growth hormone deficiency and hypogonadism have been described. However, in affected infants, thyroid function has not been well studied. The aim of this study was to analyze hypothalamo-pituitary-thyroid function during the first 2 y of life in PWS patients.

Design: 18 patients (11males, 7 females) with fulfilled clinical criteria for PWS diagnosis, confirmed by molecular analysis, were included. Mean ± SD chronological age (CA) was 1.07 ± 0.65 y, basal serum thyroid stimulating hormone (TSH), total thyroxine (tT4) and free (f) T4 levels were determined at PWS diagnosis. tT4, fT4, T3, TSH SDS were calculated from of normal reference values. T4 and /or fT4 SDSs higher than −1.3 (< 25 perc.) with TSH SDS lower than 1.5 were considered to defined CH.

Results: 16/18 PWS patients were diagnosed as having CH. Mean ± (SD) TSH and T3 levels were within normal reference values: 2.39 ± 1.6 µUI/ml (-0.54 ± 1.24) and 1.59 ± 0.35 ng/ml (-0.28 ± 0.3 SDS) respectively. tT4: 6.81 ± 1.14 µg/ml (-2.2 ± 0.77 SDS) and fT4: 0.77 ± 0.14 ng/dl (-2.3 ± 0.86 SDS) were below the lower limit of the normal reference (25 perc.).

Conclusions: CH is a common feature in PWS patients during infancy. Pediatrician should be aware to evaluate CH in PWS, in this critical period for thyroid actions on neurological development.

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Thyroid Function in the Critically Ill Pediatric Patient

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Hypothalamic pituitary thyroid axis changes during critical illness.

Objective, Patients and methods: To describe the thyroid function of the pediatric patient with an acute critical illness, we studied 37 children (median 7.56 years; range 1.1−18.8,62% boys, median weight –0.29 SDS) admitted to the Intensive Care Unit between 7/06 and 5/07. Serum TSH, T4, T3, FT4(ECLIA Roche, Elecsys)and ATPO and ATG antibodies (Immulite/DPC) were determined at admission,48,72hours and weekly up to normalization. Children < 1year, with Down Syndrome, hepatic or renal failure and CNS surgery were excluded. PRISM score was calculated at admission. Data were compared with those of control group (CG): healthy children, FT4 and T4 (n:51), TSH (n:129) and T3 (historical cohort).

Results: 4 patients had normal thyroid profile, 1 primary hypothyroidism and 32 (86.5%) low T4, T3 and/or FT4 without increase of TSH. Initial FT4 levels were lower than CG and decreased at 2° – 3° day. TSH levels were lower than CG at admission, 2° and 3° day, rising later. During follow up 2 patients died within 24hs of admission. 3 patients were treated with l-T4 and 1 was referred to other hospital. In 25 of the 26 patients followed up thyroid function recovered completely and one patient died.

Conclusions: The study of thyroid function in these patients allowed the evaluation of changes of the thyroid axis during illness and the detection of primary thyroid disease. Most of the patients with a critical acute episode experimented transient central hypothyroidism with complete recovery.

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Homeostasis Model Assessment Index (HOMA) and its Relationship with Quantitative Insulin Sensivity Check Index (QUICKI), Stimulated Insulinemia and Serum Lipid Levels in Obese Adolescents

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Introduction: HOMA index is the most reliable and used practical model for identifying insulin resistance in children and adolescents.

Objectives: To evaluate the relationship between HOMA index and other insulin resistance indicators in obese adolescents.

Methods: Both sexes adolescents were included, from 10 to 18 years old with obesity diagnosis, which assisted to the Pediatric Endocrinology service of the Cayetano Heredia Hospital from June

2006 to June 2008. Lipid profile, glucose oral tolerance test with insulin measurement, HOMA index, QUICKI and stimulated insulinemia were determined. Insulin resistance was defined as an HOMA index ≥ 3.16 according to Keskin et al. Data was analyzed using Chi square, Pearson correlation and Student's T tests.

Results: Fourty seven obese adolescents were evaluated, with an average age of 11,6 ± 1,6 years (20 women and 27 men), the Z-score for height was −0.017 ± 0.92, 70.2% (33) were pubescent. Insulin resistance was present in 36,2% (17) and only one case showed glucose intolerance. A statistically significant difference was not found between HOMA index and sex, puberty stage, acanthosis nigricans on the neck, total serum cholesterol, LDLc, HDLc or triglycerides levels. A statistically significant difference was found between HOMA and stimulated insulin and QUICKI index.

Conclusions: Insulin resistance determined by a HOMA score of 3.16 is not related with lipid levels or acanthosis nigricans presence; however, it is related with stimulated insulin and QUICKI index.

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Consequence of Gender in Congenital Adrenal Hyperplasia (CAH) Screening Cut-Off Level

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The screening of CAH detects newborns (NB) affected with classic CAH to prevent salt-wasting dehydration crises and erroneous sex assignment. Measurement of 17-OH Progesterone (17OHP) is done early after birth. Cut-off levels (CL) have been correlated to birth weight, gestational age and hours of life. Recently, Todd S. Varness highlighted a reduced sensitivity in the detection of affected female NB. Our objective was to analyze if NB gender could influence both 17OHP values and recall rate (RR). GA: Term NB born between May 2005 and April 2007, n = 14,470; n = 7,163 were girls (49.5%). GAR: Infants with 17OHP levels above the CL recalled but healthy n = 181; n = 71 were girls (39.2%). GAN: Another subgroup of samples with 17OHP below CL, n = 2,854; n = 1,389 were girls (48.7%). Sex distribution (%) was evaluated: GAN vs. GA and GAR (proportions tests*). The RR for each sex was calculated in group GAR. Additionally, 17OHP levels in GAR and GAN were compared according to gender (t-test†). Measurements of 17OHP levels (nM) were done with DELFIA–PE. GA vs. GAN (sex: boys vs. girls = ns*). A different sex distribution was found comparing GAR vs. GAN ($p < 0.05$*). In GAR the RR = 0.99% in girls and RR = 1.5% in boys ($p < 0.05$*) and 17OHP levels (x ± sd) in girls: 62.1 ± 21.6 and 75.7 ± 49.8 in boys ($p = 0.03$†). In GAN 17OHP in girls: 10.6 ± 7.6 and 12.0 ± 7.9 in boys ($p < 0.01$†). A significant influence of gender on 17OHP levels and on RR was found in neonatal screening. More studies are necessary to justify and define a scheme of cutoff levels adjusted to this parameter.

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A Longitudinal Comparison of Insulin Dynamics in Adolescents at High Risk for Polycystic Ovary Syndrome vs. those at Risk for Type 2 Diabetes

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Androgen excess in PCOS may emerge during puberty, promoted by associated insulin resistance (IR). Physiologic IR in mid-puberty generally resolves by late adolescence; girls predisposed to PCOS may fail to remit pubertal IR, leading to adult reproductive derangements. Our longitudinal survey of insulin dynamics in girls at risk for PCOS reveals differences through Tanner 3 (T3) between girls (8−14years) at risk for PCOS(N = 53) as a function of the PCOS proband glucose tolerance (GT) status, and in contrast to matched girls predisposed to T2DM (N = 17).

Methods: Annual IV GTTs were conducted among pubertal cohorts at-risk for PCOS-normal GT[PCOS-NGT]&PCOS-glucose intolerance[PCOS-GI], and contrasted with matched subjects at risk for T2DM.

Results: Unsegregated by proband GT, girls predisposed to PCOS are more insulin sensitive (SI) with inferior β-cell compensation (DI) than girls predisposed to T2DM. PCOS-GI subjects demonstrate indistinguishable mean SI and compromised DI vs. girls at risk for T2DM; conversely, PCOS-NGT subjects demonstrate superior SI and equivalent DI vs T2DM-risk subjects. Girls predisposed to T2DM decline in SI through T3; however, we observed maximal IR at Tanner 1, statistically invariant SI and deficient DI through T3 in girls predisposed to PCOS-GI.

Conclusions: Longitudinal analysis of girls at risk for PCOS demonstrates a profound effect of proband GT on subject SI and DI: those at risk for PCOS-GI exhibit maximal IR and compromised DI at T1 and through T3, in excess of that observed in obese girls at high risk to develop T2DM.

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Case Report. CYP17A1 Gene Mutations Causing Congenital Adrenal Hyperplasia

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A 15yo female complained of primary amenorrhea and lack of pubertal development as well as persistent headaches and dizziness. She had a normal female phenotype, with no evidence of adrenarche or thelarche. Lymphocyte karyotype was 46 XY. Pelvic ultrasound showed no müllerians structures. A laparoscopy demonstrated the gonads to be bilaterally placed in the inguinal canal with respective vas deferens. A 7cm vagina with a blind pouch end was found. No müllerians structures were seen. Pathology of resected gonads revealed testes with no epididimis, no vas deferens, with few Leydig cells and tubular atrophy. Hypertension was evident after surgical procedure. A 17-hydroxylase deficiency in a male genotype patient was then suspected by elevated levels of aldosterone (240 pg/ml), deoxycorticosterone (398ng/dL), pregnenolone (300ng/dL)g/dl) and progesterone (10.4ng/mL) with a high progesterone/17-hidroxyprogesterone ratio. Molecular study revealed a heterozygous component for two mutations of the CYP17 gene, a nonsense mutation in exon 2 consisting of a T insertion in the nucleotide 2758 shifted a lysine residue (AAG) to a stop codon (TAA), designated as K110X and other missense mutation in exon 6 consisting of a transition from G to A at nucleotide 5555 shifted an arginine residue (CGC) to a histidine (CAC), designated as R362H, which had not been previously described. Analysis of mutations revealed a heterozygous component for the mutation K110X in the mother and R362H in the father. We reported 2 novels mutations in the CYP17 gene in a Mexican adolescent.

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Comparative Study of the Distribution of Vitamin D Receptor Polymorphic Sites in Turner Syndrome

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Introduction: Turner syndrome (TS) patients usually suffer from secondary osteoporosis. This work is a comparative study about the distribution of different vitamin D receptor (VDR) polymorphisms in order to know if each one or within haplotypes, could be related to bone mineral density (BMD) or to any bone marker or parameter related to Ca and P metabolism in TS.

Methods: Amplification of DNA from 65 TS patients (15 ± 7 y.o) and 68 healthy individuals (17 ± 8 y.o) by PCR and digestion with Bsm I, Apa I and Taq I restriction enzymes. Determination of BMD and serum Ca, P, PTH, osteocalcin and ß-crosslaps.

Results: Genotype distribution of Bsm I and Taq I sites was similar in TS patients and controls, whereas Apa I genotypes were differently distributed within the two groups (TS: AA 15%, Aa 63,3% vs controls: AA 41,1 %, Aa 37,5%; $p < 0,01$). Bsm I bb genotype was associated with lower BMD ($p = 0,001$) whereas the other genotypes did not show association with BMD. Bone markers and parameters were similar for all groups. We detected 17 haplotypes, BbAaTt being the most frequent.

Conclusion: bb genotype is associated with lower BMD in TS. By enlarging the number of patients, we could identify some haplotypes valuable as predictors of bone deterioration.

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Metabolic Profile of Berardinelli-Seip Syndrome Patients Followed at Instituto da Criança-HC-FMUSP

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Introduction: The Berardinelli-Seip Syndrome (BSCL) is a rare congenital lipodystrophy, autosomal recessive inheritance, characterized by near absence of adipose tissue and marked hypertriglyceridemia, ectopic fat storage that lead to hepatic steatosis, insulin resistance, diabetes and atherosclerosis very early in life. In most reported cases, BSCL is due to mutations at AGPAT2 gene (9q34) and BSCL2 gene (11q13). Recently, a new mutation was report in the gene Cav-1, located at 7q31.1.

Objective: Analyze the metabolic profile of BSCL patients followed at Pediatric Endocrinology Ambulatory of Instituto da Criança-HC-FMUSP.

Pacients and Methods: The patients with clinical features consistent with BSCL were evaluated with laboratory dosages of serum fasting glucose and insulin, lipid profile, leptin, liver enzymes as well as DNA analysis and abdominal US.

Resultados: Eight children were avaluated, all girls. The average of age was 12.1 years (6.4–22). Five have mutation in AGPAT2 gene and one of them in Cav-1 gene. The other two pacients are weiting for results. Leptin deficiency was present in all cases (< 0,6 ng/ml-IFMA), one of which is diabetic and six have hyperinsulinism (fasting glucose to insulin ratio < 7). Seven patients did present hypertriglyceridemia, mean: 693,5 (128–2223 mg/dl-enzimatic assay) and in three of them, the US showed signs of hepatic steatosis.

Conclusion: the metabolic profile of patients was consistent with the latest data from the literature.

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Lipid and Glicidic Profile in Turner Syndrome (TS) Patients Associated with Birth Weight and Length, and with Current Body Mass Index

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To analyze the association between lipid and glicidic profile and current body mass index (BMI) or birth weight and length in TS patients. Sixty-four TS patients not treated with growth hormone, aged 11−29,3yr (20,4 ± 5,3yr) underwent anthropometric evaluation (weight, height and current BMI), glucose, insulin (HOMA-IR), and lipid assessment (total cholesterol and tryglicerids). To evaluate the differences in lipid and glicidic profile between body weight (z < or = -2 or > -2 SDS), birth length (z < or = -2 or > -2 SDS) and current BMI (BMI < or = 25 or > 25 kg/m2) groups, Mann-Whitney test was performed, with a level of significance of 5%. Birth weight varied from 1,14 to 4,24 kg (z < or = -2, n = 22 and z > -2, n = 42), birth length from 41 to 52,5 cm (z < or = -2, n = 40 and z > -2, n = 24) and current BMI from 15,2 to 37,1 kg/m2 (BMI > 25, n = 14 and BMI < or = 25, n = 50). There were significant differences in HOMA-IR (p = 0,005), total cholesterol (p = 0,0001) and tryglicerids (p = 0,0001), in such a way that the highest values were in low birth weight group. The same pattern was encountered in birth length, with the exception of total cholesterol [HOMA-IR (p = 0,002); total cholesterol (p = 0,345); tryglicerids (p = 0,001)]. Concerning current BMI, there were significant differences in total cholesterol (p = 0,001) and tryglicerids (p = 0,0001), in such a way that the highest values were in high BMI group, but not related to HOMA-IR (p = 0,188). We conclude that lipid and glicidic profile in TS adolescent and young adult patients were associated with both current BMI and birth weight and length.

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An Unusual Presentation of Noonan Syndrome with Hypertrophic Myocardiopathy: Mutation in the Gene RAF1

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Noonan syndrome is one of the non-chromosomal genetic syndromes most frequently associated with congenital heart defects. During the recent years a series of mutations were described as being common to various syndromes, such as Noonan, Costello, Cardiofacio-cutaneous (CFC) and Leopard syndromes. We report a patient of 1 year and 9 month of age, referred from cardiology for a phenotype compatible with this genetic syndrome, plus hypertrophic cardiomyopathy (HCM). He is the 4th child in the sibship, born at 33 weeks of gestation; severe polyhydramnios was present as well as gestational diabetes in the mother. Distinctive findings were: single umbilical artery, macrocephaly, promimnent metopic suture, protruding eye globes, nystagmus, low-set earlobes, short hyperextensible fingers, left cryptorchid testicle, short stature, developmental delay and hypertrophic cardiomyopathy. Molecular studies did not disclose mutations in the coding regions of genes HRAS; BRAF; MEK1 and KRAS, previously reported in cases of Costello and CFC syndromes. In additional studies, no mutation was disclosed in the genes PTPN11 and SOS1. An heterozygous mutation was found in the gene RAF1 causing an aminoacid change of Ser257Leu. This mutation has been described in 2007 in Noonan as well as in Leopard syndromes. It is noteworthy that while about 19% of Noonan syndrome patients may have HCM, those carrying a mutation in this particular gene present HCM in 76% of cases. We suggest that mutations in the RAF1 gene should be sought in patients with phenotypes compatible with Noonan syndrome plus HCM.

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Gonadotropin Secretion Profile in Agonadal Boys; from Birth to Puberty

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A preliminary study in 9 agonadal boys demonstrated that gonadotropins have similar changes with age and pubertal stage as in normal boys, but with higher levels. Gonadotropin ultrasensitive assays detected agonadism even in prepubertal boys. The limit of the study was the small sample.

The aim of this study was to describe the changes in gonadotropin serum levels in a larger sample of anorchid boys from birth to puberty.

We retrospectively analyzed serum concentration of basal FSH and LH (IFMA) in 29 anorchid boys confirmed by no detectable anti-Müllerian hormone (21 with longitudinal follow-up).

Between 0 and 6 months (n = 3) LH (median, range) was 73.3 IU/L (39.6−91.6) and FSH 137 IU/L (98.6−137.1). Between 6 months and 4 years (n = 9) LH was 7.2 IU/L (0.5−11.6) and FSH 60.8 IU/L (6.3−130). Up to 4 years gonadotropins were elevated for age in all cases. Between 4 and 10 years (n = 16) LH was 0.30 IU/L (0.05−8.2) and FSH 11.5 IU/L (1−59.7). In this group, 10 patients had at least one normal LH value and 4 patients had at least one normal FSH value. In patients older than 10 years (n = 13), LH was 25 IU/L (8.1−58.1) and FSH 73.9 IU/L (35.5−125). Only one patient had normal LH.

In conclusion, most of the patients with anorchia have elevated gonadotropins between birth and puberty. However, between 4 and 10 years, a nadir is observed, where gonadotropins can even fall within the normal range in some patients. In this period of life normal gonadotropins do not rule out anorchia.

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Evaluation of Insulin Sensitivity and IGFs System in Girls with Precocious Pubarche with and without Biochemical Adrenarche

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Premature pubarche (PP) is due to an early maturation of the adrenal. IGF1 has been proposed as a trigger of normal adrenarche. Alterations in insulin sensitivity (IS) and in the IGFs system have been postulated as being involved in the pathogenesis of premature adrenarche.

Aim: To study girls with PP with and without biochemical adrenarche (BA) and assess whether they present alterations in the IGFs system or in IS.

Thirty one girls with PP were studied and divided into two groups according to DHEAS level, without BA (DHEAS < 400ng/ml, PP1: 14 girls, age 6.3 ± 0.2 y. (x ± SEM) and with BA (DHEAS≥ 400ng/ml, PP2, 17 girls, 7.8 ± 0.2 y.). Both groups were compared to 34 normal prepubertal girls. C1: n = 27, 7.0 ± 0.2 y. without AB and C2: n = 7, 9.4 ± 0.6 y. with AB). The following variables were measured: serum glucose, insulin (ICMA), IGF1 (RIA), IGFBP1 and IGFBP3 (IRMA). Insulin sensitivity was assessed using fasting G/I ratio and HOMA. Two way ANCOVA was used and the covariables were the CA, SDS BMI and height SDS.

The BMI (SDS) was greater in PP1 (1.46 ± 0.35) and PP2 (1.01 ± 0.42) than in C1 (0.17 ± 0.13) and C2 (-0.21 ± 0.31) ($p < 0.05$). No significant differences were seen in insulin, IGF1, IGFBP1, IGFBP3, fasting G/I or HOMA between PP1 and PP2 vs C1 and C2.

Conclusion: In concordance with previous reports girls with PP with and without biochemical adrenarche have a larger BMI than normal. However, in contrast to what has been reported, when the results were corrected by the above mentioned variables, no alteration in insulin sensitivity or in the IGFs system were detected.

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Association of Pseudohypoparathyroidism Ia (PHP Ia) with Pseudo-Obstructive Intestinal Pathology

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Introduction: PHPIa associates resistance to the PTH and other hormones to Albright osteodystrophy(AHO). An unusual clinical presentation is described comprising anatomo pathologic findings which have not been described previously.

Methods: retrospective analysis of the clinic history.

Results: One month old baby who alternates explosive diarrheas with sub-occlusive intestinal episodes which determines an exploratory laparotomy procedure, including intestinal biopsies. Hystology shows multiple small ganglionar cells in mienteric plexus, positive with neurono-specific enolase and compatible with type A neuronal dysplasia. The patient's intestinal symptoms disappear after 6 months, and there is an important weight gain (13.2kg, BMI 25).

PHP Ia was diagnosed on the basis of physical signs suggesting AHO in the patient and in the mother. The clinical analysis shows, TSH:36.18 uUI/ml (1.0.-5); T4: 5.20 ug/dl (6−12); T3:1.48 ng/dl (0.8−2.2), Ca T: 6.7 mg% (8.5−10.5); Ca iónico: 4.1mg% (4.25−5.25), P: 9,9 mg% (4.5−6.2); PTH: 660 pg/ml (20−75).

Conclusions: PHP Ia and type A neuronal dysplasia are two low incidence pathologies and an association between them has not yet been characterized.

The intestinal pseudo-obstructive pathology has been described in patients with pathologies with elements similar to PHP 1a such as hypothyroidism and hypoparathyroidism. This together with the recent publication of a patient with PHP Ia accompanied by neonatal diarrhea, suggests future histological studies will establish if there is connection between findings described for our patient.

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Daily Energy Balance (EB) in Overweight Teenagers

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Aims: To evaluate daily caloric intake and expenditure and the factors associated with the energy imbalance of overweight adolescents.

Materials and Method: In 158 adolescents (84 males) with BMI ≥ 85 th percentile (14.2 to 15.6 years), we evaluated the socioeconomic level (SEL) by Graffar and the magnitude of the overweight by BMI z (CDC / NCHS). The % of fat-free mass (FFM) and body fat (BF) by isotope dilution (Deuterium), daily caloric intake (CI) and physical activity (PA) by record of 24 hrs, the adequacy of CI (ACI) and the Index PA (IPA) by FAO / WHO, the basal metabolic rate (BMR) by indirect calorimetry, the total caloric expenditure (TCE = BMR*IPA) and daily caloric retention (CR = CI-TCE) were estimated. We used to chi2 by associations, and ANOVA and Bonferroni to compare averages and Pearson and Spearman for correlations.

Results: The zBMI was lower ($p < 0.05$) and FFM % was higher ($p < 0.01$) in the high SEL, with no differences in %BF. The ACI was < 78% of FAO/WHO sedentary population recommendations, the IPA has fluctuated between 1.26 and 1.34 and the CR between 364 and 395 Kcal, without differences by SEL. The 78.7% of the CR could be explained by zBMI, FFM% and ACI.

Conclusion: In overweight adolescents, the daily EB shows no differences by SEL. The CI and the IPA are under the sedentary populations recommendation and there is an important CR that is directly associated with body weight and inversely with the CI and FFM%.

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Differential Diagnosis of Sexual Precocious Development in Girls: Basal LH vs GnRH Test with Ultrasensitive Assays

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Introduction: One of the main tools in diagnosing Central Precocius Puberty (CPP) is the (LH/FSH)max ratio post GnRH administration, considering it puberal beeing > 0,30 (DELFIA assay).

Objective: to compare a chemolumniscensce assay (ICMA) with DELFIA and to evaluate diagnosis efficiency of basal LH by ICMA.

Methods: Funtional sensibility (FS) for LH and FSH by ICMA (Immulite, DPC) was evaluated. LH and FSH values post GnRH by ICMA and DELFIA were compared in 15 girls with isolated telarche (IT) and 21 girls with CPP (diagnosis based on clinical data and LH max post GnRH > 5 UI/L by ICMA). Correlation and concordance coefficients for LH and FSH between both methods were determined in 100 tests'samples. ROC curve analysis was used to determine sensibility (S) and specificity (E) of basal LH by ICMA vs (LH/FSH) max ratio by DELFIA to predict CPP.

Results: FS for LH and FSH by ICMA was 0.43 y 0.27 IU/L respectively. Correlation and concordance coefficients for LH between both methods were 0.983 and 0.969. Correlation coefficient for (LH/FSH)max ratio between both methods was 0.95. A basal LH value by ICMA > 0,43 UI/L identified CPP patients with a S = 77% and E = 93% (area under the curve 0,87).

Conclusion: LH and FSH determinations by ICMA are comparable with IFMA for values above ICMA's FS. Basal LH by ICMA may contribute in the diagnosis of CPP with a S: 77% and E: 93% when the GnRH test is not available.

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Risk Factors for the Development of Early Obesity

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In Mexico, the prevalence of overweight and obesity in pre-school children have increased of 5,3% in 1999 to the 9,4% in the 2006. Considering the mechanisms that limit the fat gain in this stage, these data are impressive. Factors related to the intrauterine and postnatal environment like the maternal obesity and hyperglucaemia, high and and low birth weight, the early weaning, breast-feeding, the sugar-sweetened beverages ingestion, among others are considered risk factors for early obesity.

Methods: In order to find the relative contribution of prenatal, postnatal and genetic factors in the development of obesity we studied patients with diagnosis of obesity before the age of five years and compared with children older than 5 years old without overweight. Risks by means odds ratios were calculated for each one of the studied factors

Results: We studied 90 children with obesity and 20 children with overweight developed before the 5 years of age and 90 children older than 5 years without overweight. We find significant differences for the familiar antecedent of obesity (p = 0−00), macrosomia and gestational diabetes in their mothers (p = .02), as well as the early whole milk introduction (p = 0−04). The familiar antecedent of obesity increases 4,14 times the risk for developing early obesity, whereas the antecedent of gestational diabetes increases 1,16 times.

Conclusions: The identification of risk factors during the intrauterine life and in the first months of extrauterine life will allow to establish opportune preventive strategies.

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Expression and Activity of 11β-OH-Steroid Dehydrogenase (11β-HSDs) Type 1 and 2 Enzymes in Human Term Placenta from Small (SGA), Appropriate (AGA) and Large (LGA) for Gestational Age New Borns

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Introduction: In some species foetuses with growth restriction have higher glucocorticoid systemic concentrations. The bioavailability of cortisol at the placental level is regulated by the 11β-HSDs which converts cortisone to cortisol (11β-HSD1), and cortisol to cortisone (11β-HSD2).

Objective: To study the expression of 11β-HSDs in full term placentas from SGA, AGA and LGA newborns and the cortisol cord blood concentration.

Methods: We selected 15 AGA, 15 SGA and 17 LGA. 11β-HSDs placental expression and activity, were determined in the maternal

	Placental side	SGA	AGA	LGA
11β-HSD1/ 18S rRNA	Maternal	0,32±0,06	0,29±0,06	0,28±0,04
	Fetal	0,21±0,04*	0,25±0,05	0,26±0,04
11β-HSD2/ 18S rRNA	Maternal	0,37±0,04	0,43±0,06	0,44±0,07
	Fetal	0,35±0,06	0,43±0,08	0,38±0,05
11β-HSD1 activity (pg/min/mg protein)	Maternal	0,97±0,08	1,26±0,15	1,06±0,08
	Fetal	0,93±0,06**	1,41±0,14	1,25±0,13
11β-HSD2/ 18 S rRNA (pg/min/mg protein)	Maternal	8,7±1,0	8,6±0,8	10,4±1,1
	Fetal	9,0±1,2	7,9±1,0	9,0±0,8
Cortisol (µg/dL)		16,0±1,9***	11,0±0,7	10,3±1,0

*p < 0,05 M vs. F; **p < 0,05 SGA vs AGA; ***p < 0,05 SGA vs. AGA and LGA.

(M) and fetal (F) side of the placentas, by RT-PCR and by HPTLC respectively. Cortisol was determined by RIA.

Results: Are shoen in the table as mean ± SEM).

Conclusion: The lower expression and activity of 11β-HSD1 observed in the fetal side of the SGA placentas suggests a possible compensatory mechanism to diminish the higher cortisol fetal concentrations observed in foetuses with intrauterine growth restriction.

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Effect of Growth Hormone (GH) Treatment to Idiopathic Short Stature (ISS) Patients on Peripheral Thyroid Hormone (TH) Mechanism of Action

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Introduction: In previous studies we demonstrated that GH administration to experimental animals and to Turner Syndrome Patients reduced TH mechanism of action evaluated through the expression of its nuclear receptors (TRa and b) and serum markers of TH action (SHBG and TSH). The aim of this work is to study the response to TH in ISS patients under GH therapy. In ISS the height of the individual is more than 2.5 SD below the mean height for a given age, sex and population with no identifiable disorder. Several clinical trials demonstrated beneficial effects of GH treatment.

Patients & Métodos: Five ISS patients that exhibited a growth velocity (GV) < 2.5 SD and positive GH generation tests were evaluated and analyzed previous (pre) and after (post) 12 months of GH therapy (1UI/kg/week). Peripheral blood mononuclear cells were obtained and total RNA extraction for the expression of TRb and a (real-time RT-PCR) performed. In turn, SHBG and TSH were measured in serum (electrochemiluminescence)

Results: The results achieved in post samples (vs. pre samples designed as 1.00) were: TRb: 0.44 ± 0.19; TRa: 3.12 ± 1.60; SHBG: 0.73 ± 0.06; TSH: 1.87 ± 0.50 (test t, $p < 0.05$)

Conclusions: These results indicate that GH treatment to ISS patients reduced the expression of TRb and enhanced that of TRa. In agreement, a reduction of SHBG and an increase of TSH serum levels were recorded. These preliminary results are being analyzed in a larger number of patients. Since the bone is a target tissue for TH action, these findings may have repercussions in the growth response to GH therapy

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Autoimmune Polyglandular Syndrome Type 1 (APS1) in an Argentine Patient: Clinical Characterization and a Novel Mutation in the Autoimmune Regulator (AIRE) Gene

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Introduction: APS1 is a rare organ-specific autoimmune autosomal recessive disease associated with mutations of the AIRE gene.

Subjects and Methodology: We investigated a 4-year-old boy under treatment for hypoparathyroidism. Each exons of the AIRE gene were individually PCR-amplified, purified, and sequenced by a DNA autosequencer.

Results: The patient presented mucocutaneous candidiasis since the age of 3. He manifested malabsorption symptoms, with negative anti-gliadin, anti-endomysial and anti-smooth muscle antibodies (Abs). Gastro-esophageal endoscopy showed esophagitis by Candida, chronic gastritis and duodenitis. In addition, he developed Sjögren Syndrome and vitiligo in face, trunk and limbs. The patient displayed persistence of hypertransaminasemia with positive anti-liver-kidney microsomal Abs. A hepatic biopsy showed mild active chronic hepatitis. He presented positive adrenal cortex Abs with normal serum cortisol and ACTH. Because of the presence of two diagnostic criteria of APS1, the molecular study of the AIRE gene was performed. A novel heterozygous 2-bp deletion in exon 8 (c901−902delGT) was detected. This mutation presumably results in a frameshift at C302 and premature truncation of a 311-amino acid protein with 9 C-terminal amino acids unrelated to the normal AIRE protein. Moreover, a previously TGT (X546C), was detected in→described mutation in the stop codon of AIRE, TGA the other allele.

Conclusions: A novel AIRE gene mutation was identified. This is the first molecular study reported in a patient with APS1 from Argentina.

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Serum Homocysteine Levels in Children Born Small for Gestational Age

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SGA children have increased risk of developing obesity, insulin resistance and cardiovascular disease (CVD) in later life. Leptin and homocysteine (Hcy) are potencial biomarkers for predicting the risk of CVD. In hyperinsulinemic obese children and adults elevated total Hcy levels has been found. Few studies have examined Hcy levels in SGA children. We aimed to study total Hcy levels in SGA children with and without catch up growth and assess to their possible association with leptin and insulin sensitivity parameters. We analyzed 21

SGA children with catch up growth (SGAcg), CA 7.0 yr SDS height −0.88 and 23 SGA children without catch up growth (SGA –cg) CA 6.1 yr SDS height −2.27 and 39 healthy children born appropriate for gestational age (AGA), CA 7.2 yr SDS height −0.16. Hcy, proinsulin, leptin, IGFBP-1, insulin levels, HOMA-IR and HOMA ß cell were measured. ANOVA and Spearman correlation were used.

Results: nonsignificant differences were found in Hcy mean values between SGA and AGA childrens (9.1, 7.7 y 7.8 µmol/l en SGAcg, SGA-cg and AGA respectively) No significative correlation between Hcy levels, birth weigh, BMI, leptin and insulin sensitivity parameters analized, were found.

Conclusions: Our study shown that prepubertal SGA children with normal weight, Hcy levels do not resulted a biomarker for differenciated between the analized groups. Longitudinal further studies of metabolic parameters in this cohorte with different ponderal recuperation should be evaluated for assess to possible effects in the deveplopment of metabolic diseases.

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An International Comparison of the Prevalence of Metabolic Syndrome Risk Factors Among Obese Hispanic Adolescents with Polycystic Ovarian Syndrome

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Background: Adult women with polycystic ovary syndrome (PCOS) have an increased prevalence of the metabolic syndrome (MS) yet few studies have evaluated the prevalence of metabolic syndrome risk factors (MSRF) in adolescents with PCOS, and by ethnicity in particular.

Methods: The aim of the current analysis was to estimate/compare the prevalence of MSRFs among Hispanics (ages 12−18) with PCOS residing in Mexico City (n = 38) and Miami, Florida (n = 57). Analysis of anthropometric (body mass index [BMI], waist circumference [WC]), and laboratory data (fasting insulin, glucose, total cholesterol, triglyceride) using medical charts among girls attending an obesity clinic at Children's Hospital in Mexico City, and Hispanic girls at the University of Miami, was conducted. PCOS diagnosis was established if 2 of the following: (1) clinical/biochemical hyperandrogenism, (2) PCO by ultrasound, or (3) oligo-anovulation.

Results: Mexican girls had significantly higher mean triglyceride (164.31 vs. 107.94 mg/dL, $P < 0.001$) and cholesterol (168.47 vs. 164.68 mg/dL, NS) versus Miami girls who in turn had significantly higher fasting insulin (30.14 vs. 19.59 mIU/mL, $P < 0.05$), BMI (38.19 vs. 29.18, $P < 0.0001$) and WC (113 vs. 96 cm $p < 0.001$).

Conclusions: PCOS is associated with MSRF in adolescents from various Latino backgrounds. However, individual MSRF vary by specific ethnicity indicating that PCOS may have strong environments and genetic attributes. Hypertriglyceridemia associated with lower insulin response in Mexican girls may predict a stronger cardiometabolic risk outcome.

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Influence of Polycystic Ovarian Syndrome on the Prevalence of Metabolic Syndrome Risk Factors Among Obese Hispanic Adolescents

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Background: Polycystic ovarian syndrome (PCOS) is a leading cause of cardiometabolic disease in adolescent girls, particularly among those who are obese. Previous studies suggest that adolescent girls with PCOS have a higher prevalence of the metabolic syndrome (MS) compared to the general adolescent population but little comparison has been done with their obese non-PCOS counterparts.

Methods: The aim of the current analysis was to estimate/compare the prevalence of MS risk factors among 4 obese Hispanic (ages 12−18) groups: those with (n = 38) or without (n = 31) PCOS residing in Mexico City, and in Miami, Florida (n = 57 and 89, respectively). Analysis of body mass index (BMI) waist circumference (WC), and fasting insulin, glucose, total cholesterol and triglycerides using medical charts among girls attending an obesity clinic at Children's Hospital in Mexico City, and Hispanic girls at the University of Miami, was conducted. PCOS diagnosis was established if 2 of the following: (1) clinical/biochemical hyperandrogenism, (2) PCO by ultrasound, or (3) oligo-anovulation.

Results: Mexican girls with PCOS had significantly lower fasting glucose (83.15 vs. 92.35 mg/dL, $p < 0.01$) and higher waist circumference (95.98 vs. 87.01cm, $p < 0.05$ compared to their non-PCOS counterparts. Miami girls had significantly higher BMI (38.19 vs. 31.20, $p < 0.0001$) and WC (113.48 vs. 97.29 cm, $p < 0.0001$) than their non-PCOS counterparts.

Conclusions: Abdominal adiposity is predominant in both groups of PCOS patients suggesting that hyperandrogenism may exert direct effects on body fat distribution

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Waist to Height Ratio and Cardiometabolic Risk in Adolescents with Obesity and Overweight

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Introduction: The estimate of cardiovascular risk in children and adolescents with overweight has taken great significance for increasing prevalence of obesity worldwide. In Japanese adults and children in Europe and Asia have conducted studies documenting the Waist to Height Ratio as better predictor of cardiovascular risk factors than the body mass index and abdominal perimeter.

Methods: We evaluated 103 adolescents of both sexes, with an average age of 14.04 ± 1.52 years, 68 obese and overweight 45. We performed waist and height measuring and correlated with HOMA, QUICKI, Triglycerides / HDL indexes, lipid profile and Fibrinogen.

Results: Waist to height Ratio correlates significantly with triglycerides, HDL levels and HOMA, QUICKI and Triglycerides / HDL indexes.

Conclusion: Waist to height Ratio is a practical, simple and useful in predicting cardiovascular risk factors in adolescents with obesity and overweight.

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Androgen Receptor Gene Expression in Genital Tissues and Peripheral Blood Lymphocytes

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Hypospadias can be determined by failure on androgen production or action upon its receptor (AR). The aims of this study were to develop a quantitative method for AR gene expression by employing real time PCR, allowing the measurement of AR expression in prepubertal genital tissues (preputial skin and urethral mucosa) and peripheral blood lymphocytes. The samples were obtained from boys with phimosis (n = 28) and boys with idiopathic hipospádia (n = 8). qRT-PCR was performed in Applied Biosystems 7500 thermo-cycler, employing FAM-labeled TaqMan probes. Standard curves were constructed with RNA obtained from normal prostate gland of cadaver donor. In order to normalize for the amount of RNA, absolute AR quantitation was corrected for the expression of the constitutive gene BCR, AR/BCR quantitative ratio (see Table). The results are presented as median (interquartile).

	Phimosis	Hypospadia
AR/BCR blood	0.3(0.2–1.5)*	0.6(0.10−1.5)*
AR/BCR urethra	40.3(17.4−62.3)	32.8(22.8−37.0)
AR/BCR prepuce	25.5(6.1−42.2)	14.9(9.9−22.0)

The expression of the androgen receptor gene was reduced in peripheral blood lymphocytes when compared with the other genital tissues (*$p < 0.05$, Mann Whitney). The qRT-PCR proved to be vey efficient in the measurement of the AR gene expression. Additional patients should be studied, in order to rule out the quantitative failure of gene expression as a putative mechanism of idiopathic hypospadia.

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