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ASSESSMENT OF THE HYPOTHALAMIC PITUITARY ADRENAL (HPA) AXIS: INSULIN INDUCED HYPOGLYCEMIA VERSUS PAIN. CE Hanna, SH Mandel, BA Boston, SH LaFranchi, Department of Pediatrics, Oregon Health Sciences University, Portland, OR 97201, USA

To compare the cortisol response to insulin induced hypoglycemia and pain, we carried out a retrospective analysis of 351 short children who underwent growth hormone (hGH) testing with insulin induced hypoglycemia and arginine between 7/75 and 6/92. A venous catheter was placed (pain stimulus) 30 to 60 minutes prior to the test. At 8 a.m. the fasting child received insulin, .05 to .1 unit/kg, (↓ glucose stimulus). A serum cortisol was measured following pain at 8 a.m. and following insulin at 9 a.m. Children were judged to have an adequate ↓ glucose stimulus if the blood sugar fell 40% and or reached a glucose nadir ≤ 45 mg/dl. Of the children with an adequate ↓ glucose stimulus, 102 were hGH deficient (hGH ≤ 7 ng/ml), while 75 were hGH sufficient (hGH > 10 ng/ml). The peak cortisol level in the hGH sufficient children who had no clinical features of HPA axis dysfunction was 23.3±7.2 mcg/dl (mean ±1 S.D.). A cortisol response ≥ 9 mcg/dl (mean-2 S.D.) in our hands is the normal response to pain/hypoglycemia, considerably lower than the traditional 18 mcg/dl cutoff established in adults. A peak cortisol value in the 9-18 mcg/dl range may represent partial ACTH deficiency or may be normal (21% of the hGH sufficient children fell in this range).

	% with cortisol ≥ 9 mcg/dl			% with cortisol ≥ 18 mcg/dl		
Stimulus	pain	↓ glucose	either/or	pain	↓ glucose	either/or
hGH sufficient	87	96	100%	23	69	79
hGH deficient	77	87	90%	34	55	68

We conclude that the HPA response to pain/hypoglycemia in normal children is lower than previously reported. Hypoglycemia was statistically ($p < .001$ in normal children, $p < .01$ in hGH deficient children) more likely to stimulate a cortisol value ≥ 18 mcg/dl than pain.

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THE HETEROGENEITY OF 3ß-HYDROXYSTEROID DEHYDRO GENASE (3ß-HSD) DEFICIENCY- REPORT OF 4 CASES. U.Heinrich,M.Bettendorf,J.Grulich-Henn,D.Schönberg, J.Simard and F.Labrie. Dep. of Ped. Endocrinol., Univ. Children's Hosp., Heidelberg, Germany;MRC Group in Molec. Endocr. CHUL Res. Ctr. and Laval Univ. Quebec, Canada.

In male infants variable degrees of sexual ambiguity and salt loss are typical features of 3ßHSD deficiiency.- We have observed 4 patients with unequivocal 3ß-HSD deficiency, 3rd degree hypospadias,but largely different hormonal and clinical pattern. Case1(Turkish origin) : markedly elevated 17OHPreg(Preg),nl Cortisol (F), ACTH, no salt loss. Case 2(German origin):17OHPreg clearly elevated,nl F and ACTH, moderate salt loss. Case 3 (Afghani origin):high 17OHPreg,high ACTH,low F,severe salt loss.Case4(German origin) congenital hypothyreoidism, high stimulated 17OHPreg and DHEA despite DEXA treatment (0.3 mg od for BPD),salt loss.

ACTH	F 0'	F 60'	Preg 0'	Preg60'	DHA 0'	DHA 60'	salt loss
test	ug/dl	ug/dl	ng/dl	ng/dl	ng/dl	ng/dl	
pt 1	15.6	23.4	2226	21597	470	2603	-
2	15.9	25.4	408	2247	125	547	(+)
3	1.0	0.8	734	1140	231	212	++
4	18.0	37.1	82	4301	118	618	+

In case1 a homozygous missence mutation of the type II 3ß-HSD gene due to a substitution that converts Ala 245 into Pro was detected. Gene expression in non steroid-producing cells revealed an enzyme activity of ~10 % compared to the wild-type gene which could explain the patient's normal salt retaining capacity. In case 3 a homozygous point mutation of the type II gene has been detected, which has to be further evaluated. In cases 2 and 4 molecular analyses are in progress. In conclusion: The determination of the molecular basis of individual cases with evidence of 3ß-HSD deficiency will eventually lead to a better understanding of the wide heterogeneity of severe and mild forms of this disease and should provide important informations concerning the structure-function relationship of the 3ß-HSD gene family.

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DIFFERENTIAL DIAGNOSIS OF TERMINAL ALDOSTERONE BIOSYNTHESIS DEFECTS. M. Peter[1], S. Geley[2], W.G. Sippell[1] and R. Kofler[2], [1]Dept. of Paediatrics, Univ. of Kiel, Germany and [2]Inst. of Gen. and Exp. Pathology, Dept. of Molecular Biology, Univ. of Innsbruck, Austria ·

Terminal aldosterone biosynthesis (TAB) from 11-deoxycorticosterone (DOC) requires 11-hydroxylation, 18-hydroxylation, and finally oxidation at C-18. One single P450 catalyzes all 3 steps encoded by the gene CYP11B2. The two known TAB defects are characterized by excess corticosterone (B) and deficient Aldo. CMO (corticosterone methyl oxidase deficiency) type I has low, while CMO II has elevated 18-OHB levels. Since 1982, we diagnosed 3 pts with CMO I and 5 with CMO II by multisteroid analysis (RIA after extraction and automated gel chromatography). Both types could be clearly differentiated by B/18-OHB and 18-OHB/Aldo ratios which ranged 32-136 and 11.5-16.7 in CMO I, and 1.9-11.2 and 22-286 in CMO II pts, respectively. The ratio B/18-OHB appears particularly useful in CMO cases with undetectably low Aldo levels and noncalculable 18-OHB/Aldo ratios. In 2 of our 5 CMO II pts we did not find any of the 2 known mutations described in such pts from Iranian-Jewish origin. Genomic cloning and sequence analysis of the CYP11B2 genes in our CMO I and II pts may reveal the nature of the marked biochemical differences found in TAB disorders.

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R Virdis, M. Vanelli, L Ibanez, C Terzi*, M Street*, A Defanti*, M Zampolli, N Potau, L Ghizzoni, C Cantoni*, L Bonacini*, E Vicens-Calvet, S Bernasconi, G Giovannelli. Departments of Pediatrics, Univ. Parma & Autonomous Barcelona-Italy & Spain.

EVIDENCES OF OVARIAN HYPERFUNCTION IN ADOLESCENT GIRLS WITH INSULIN DEPENDENT DIABETES MELLITUS (IDDM) AND MENSTRUAL DISORDERS.

Diabetic women present an elevated incidence of mestrual disorders often associated with partial gonadotropic insufficiency with reduced LH, E2 and ovarian androgen production. Among our adolescent IDDM population 8 over 36 postmenarcheal girls (22%) complained of oligo- or amenorrhea and 4 of hirsutism also. To verify their pituitary and ovarian functions we assessed the gonadotropine and ovarian steroid response to the administration of 500 ug s.c. of GnRHa Leuprolide acetate in 7 patients with IDDM (age 17.8±1.7 yrs) and 12 age-matched normal girls. Basal and stimulated LH, FSH, E2, DEAS, T and basal 17OHP and D4-A levels were similar in the two groups, regardless of elevated baseline androgens levels in few girls. 24hr-stimulated 17OHP levels were significantly higher in patients than in controls (7.8±2.2 vs. 2.8±0.3 nMol/L, p 0.0001). D4-A responses were also higher than in controls although the difference was not statistically significant (9.8±1.4 vs. 6.1±0.7 nMol/L n.s.). This behaviour was similar to that of a previously studied group of 35 adolescents with hirsutism and ovarian hyperfunction (17OHP 7.0±0.4 nMol/L, D4-A 11.2±0.9 nMol/L). These data demonstrate the presence of a high incidence of ovarian hyperfunction in adolescent diabetic girls which can underlie the menstrual disorders. We need a follow-up of these patients to clarify whether they will develop a clear hyperandrogenisa, as suggested by our results, or a partial gonadotropin insufficiency as other observed in older diabetic patients.

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GONADAL FUNCTIONS IN 24 PATIENTS AFTER BONE MARROW TRANSPLANTATION. B LeHeup, S Denet, P Bordigoni, D Sommelet, and M Pierson Divisions of Development and Pediatric Oncology, Children's Hospital, Medical School, Nancy, France

The long term follow-up of patients after bone marrow transplantation (BMT) allows for a more precise definition of its potential side-effects. Gonadal functions are potentially sensitive to several procedures regularly used for BMT preparations, either total body irradiation (TBI) or high dose regimen chemotherapy. We present a series of 24 patients aged at least 14 years previously treated by BMT, either before or after onset of puberty. There were 17 boys and 7 girls. Mean age at BMT was 13,2 for the boys and 11,2 for the girls. 11 did not show any sign of pubertal development at the time of BMT. The indications for BMT were ALL in 11, ANLL in 2, lymphoma in 4, Chronic leukemia in 1, aplastic anaemia in 4 and solid tumors in 1. 13 received allogenic BMT and 11 autologous BMT. All the 7 girls, whatever the types of preparations and BMT, developed severe ovarian failure. Of the 17 boys, all 5 who have received previously testicular irradiation for ALL relapse and TBI before BMT have evidences of leydigian dysfunction (Δ). The evolution of the others 12 is summarized in the table according the status of puberty and conditioning regimens.

	Normal	Sertoli Δ	Leydig and Sertoli Δ
Prepubere at BMT	2	2	1
Pubere at BMT	3	1	3
Chemotherapy only	4	2	3
Chemotherapy and TBI	1	0	2

Of the 9 given chemotherapy only, 3 were prepubere at BMT and 2 of these developed Sertolian dysfunction. In conclusion, this study confirms the constant ovarian dysfunction after BMT in girls. For the boys even in the group of patients given only chemotherapy there was evidence of secondary testicular dysfunction regardless of the respective timing of BMT and the onset of puberty.

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X-LINKED CONGENITAL ADRENAL HYPOPLASIA, GONADOTROPIN DECICIENCY AND HIGH FREQUENCIES SENSORINEURAL HEARING LOSS.

R. Balducci,G. Conti*, A.M. Pasquino**,V. Toscano°,A. Mangiantini, G. Municchi**, A. Burlina+, B. Boscherini. Dept. of Pede. II Univ.; **Dept. of Pede I Univ.; °Dept.of Endocr.I Univ.;* ENT Clinic Catholic Univ. ROME and +Dept of Peds. Univ. of Padua. ITALY.

X-linked congenital adrenal hypoplasia (CAH) may occur alone or in association with hypogonadotropic hypogonadism (HH), glycerol kinase deficiency (GKD) and myopathy. The relationship between these conditions is genetic since the loci for CAH, HH and GKH are located in the same region of X chromosome. A progressive high frequency hearing loss (HL) has been recently described only by Zachmann. We report two male cousins (aged 24.2 and 21.7 yrs at last observation) with CAH, HH and an unusual tall stature. GKD was excluded by determination of plasma and urine glycerol levels. A mild bilateral HL for high frequencies was diagnosed in the younger patient at 15 yrs of age. At this time the audiogram of the older patient was normal.The hearing evaluation performed in the following years showed a progression of the HL most evident at 4KHr in the younger patient and a cochlear site of lesion was revealed by brainstem response audiometry. In the older patient, the last audiogram showed just a slight asymmetric sensorineural HL for the high frequencies (2-8 KHr). In agreement with Zachmann's report, our data show that HL may be associated with CAH and HH even if the degree of HL is unpredictable.Therefore the hearing function of these patients must be monitored.The hypothesis of a genetic basis of the relationship between CAH,HH and HL (vicinity of the locus of X-linked deafness with the loci of CAH and HH) is fashinating and requires further support.