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Male Pseudohermaphrodism due to 17,20-Desmolase Deficiency.

A 5 1/2 year old 46,XY pseudohermaphrodite presented with microphallus, third degree hypospadias, chordee and normal male internal genitalia. Serum LH and FSH levels were <1.7 mIU/ml. Results of adrenal and gonadal stimulation and Dexamethasone (DEX) suppression were:

Serum (ng/dl)	BASAL	ACTH	DEX	DEX and HCG
Progesterone	56	629	16	16
17-OH-Progesterone	350	1350	34	34
17-OH-Pregnenolone	173	225	37	42
Androstenedione	61	48	<10	<10
Testosterone	<10	<10	<10	<10
Cortisol (µg/dl)	35	46	1	.9
DHEA-S (µg/dl)	31	46	9	10
Urine (mg/24hr)				
Pregnanetriolone	.2	3.93	<0.01	0.04
DHA	<0.01	<0.01	<0.01	<0.01

In this patient the elevation of progesterone, 17-OH-Progesterone, 17-OH-Pregnenolone, and pregnanetriolone in conjunction with low DHEA-S, androstenedione, and DHA are consistent with gonadal and adrenal 17,20-desmolase deficiency which resulted in incomplete virilization.

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Diagnosis and control of treatment of congenital adrenal hyperplasia (CAH) by semiautomated capillary gas-liquid-chromatography (cGLC) of steroid trimethylsilyl-enolethers (TMSEE).

CAH due to 21-hydroxylase (21-HD), 11-hydroxylase (11-HD) or 3β-hydroxysteroiddehydrogenase (3β-HSD) deficiency can be diagnosed by detection of specific urinary steroid metabolites. Moreover, CAH-treatment can be controlled by quantitation of specific metabolites i.e.pregnane-3α,17α,20αtriol and pregnane-3α,17α,20αtriol-11 on in 21-HD, tetrahydro-11-desoxycortisol in 11-HD and Δ5pregnene-3β,17α 20αtriol and 16αhydroxy-Δ5pregnene-3β ol-20 on in 3β-HSD. We have developed a sensitive, highly specific automated method for the quantitative cGLC of TMSEE of these and other steroids. The method includes enzymatic hydrolysis, ether extraction, one-step derivatisation using N-methyl-N-trimethylsilyl-trifluoracetamid in presence of sodium acetate. The automated cGLC using solid injection separates about 10 samples/night. Because of the high resolution, no further purification step is needed. Mean coefficient of variation of the entire method is 12%. Unknown steroids can be detected by cGLC and identified by mass spectrometry. The TMSEE are convenient and stable enough for cGLC conditions. Ranges of steroid excretion in the different forms of CAH for four different age groups indicating optimal treatment have been established. In conclusion, cGLC with steroid TMSEE provides a precise, rapid and convenient tool for both diagnosis and treatment control of CAH.

120 **E.LEIBERMAN*,A.ROSSLER*,T.COHEN*,S.W.MOSES*,(Intr.by M.ZACHMANN).Dept.of Pediatrics,Soroka Med. Center,Faculty of Health Sciences Ben-Gurion Univ.of the Negev, and the Dept. of Endoc.& Genetics,Hadassa Med.School,Ein-Karem, Jerusalem. Congenital adrenal hyperplasia due to 11β hydroxylase deficiency. 25 cases of congenital adrenal hyperplasia due to 11β hydroxylase deficiency belonging to 17 families have been diagnosed in Israel.These provided an unique opportunity to study the clinical spectrum of this disease. Patients were of North-African Jewish extraction.Diagnosis was suspected by clinical evidence of premature or abnormal virilization associated in some cases with hypertension.This diagnosis confirmed biochemically by the presence of high urinary levels of tetra hydro 11 deoxycortisol.In affected females clinical expression varied from enlarged cliteris to severely hypertrophied clitoris with penile urethra and fused labial scrotal folds.10 out of 14 females who were not diagnosed early in life were reared as males,required corrective surgery at puberty. Removed ovaries showed cystic changes.In these androgen excess was uneffective in suppressing gonadotropin secretion.Hypertension was present in 15/25 cases and led to fatal vascular accidents in 3 cases.Hypokalemia,observed in 9 patients was not correlated to hypertension.Except in infants,low levels of renin activity were found in all untreated cases,indicating a state of volume expansion.No correletion was found between the degree of virilization and biochemical evidence of mineralocorticoid excess.Preliminary data on an attempt at antenatal diagnosis by measuring THB in maternal urine and fetal amniotic fluid of affected cases will be reported.**

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Late-Onset, Cryptic and Classical 21-OH Deficiency: Allelic Variants

HLA genotyping and hormonal studies in 9 females with non-classical steroid 21-hydroxylase deficiency (AAH) indicate that this disorder is due to an autosomal recessive gene linked to HLA, similar to classical and cryptic 21-hydroxylase deficiency (21-OH def). They had normal genitalia at birth and presented between 9 mos to 16 yrs with varying degrees of virilization. Hormonal studies of the families revealed 2 fathers and their HLA identical sisters with 21-OH def. The remaining parents and the sibs sharing one HLA haplotype with the AAH patient responded to ACTH stimulation as heterozygotes for classical or cryptic 21-OH def. Five sibs who were HLA identical to their affected sib also had findings diagnostic of 21-OH def. The hormonal response to ACTH of the patients with AAH and their HLA identical sibs was similar to that of patients with cryptic 21-OH def. Thus, individuals with these non-classical forms of 21-OH def and similar hormonal findings present with a clinical spectrum ranging from an asymptomatic deficiency to precocious pubic hair, acne, tall stature and advanced bone age, hirsutism, clitoromegaly and menstrual irregularities. The results of these studies support the concept that AAH, similar to classical and cryptic 21-OH def is due to an HLA linked autosomal recessive gene and that these disorders are due to allelic variants at the locus of steroid 21-hydroxylase.

122 M.I.NEW, B.KOHN*, M.POLLACK*, S.PANG, D.LEVY*, G. RONDANINI*,F.LORENZEN*,A.LERNER*, B.DUPONT*, L.S.LEVINE, The New York Hosp-Cornell Med Ctr, Sloan-Kettering Inst Cancer Research, NY USA and Univ Milan, Italy.

Genotyping for 21-hydroxylase deficiency: one or two genes?

We have devised nomograms relating the baseline and ACTH stimulable levels of 17-OHP, Δ 4-androstenedione and testosterone for genotyping 21-hydroxylase deficiency. The nomograms provide a method for classifying the patient with congenital, late onset or cryptic 21-hydroxylase deficiency as well as classifying the heterozygotes for each of these disorders. In addition, the subject predicted by HLA genotyping to be genetically unaffected can also be classified by these nomograms. Further the nomograms permit us to obtain evidence for genetic recombination between HLA and the 21-hydroxylase locus. For example a patient predicted by initial HLA genotyping to be unaffected was classified by the nomogram to be a heterozygote. When HLA-DR typing was performed an informative maternal HLA A:DR recombination was discovered. This recombination explained the heterozygote response of this subject. In another family a maternal DR:GLO recombination was found in an asymptomatic sister who was HLA identical to the patient with late onset 21-hydroxylase deficiency. Although most recombinants have mapped the gene for 21-hydroxylase between B and DR, this DR:GLO recombination presents evidence that there may also be a 21-hydroxylase locus between the DR-GLO loci. The nomograms thus provide a powerful tool to determine the 21-hydroxylase genotype by hormonal testing and assist in mapping the gene for 21-hydroxylase deficiency.

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Hypertension, hypokalemia and retarded growth in a 17 month-old boy with 11 β hydroxysteroid-dehydrogenase deficiency.

A 17 month old boy, the first child of unrelated parents, presented with polydipsia, lack of appetite and failure to thrive. Blood pressure was 150/100 mmHg. He had hypokalemia (2.6 mEq/l), suppressed renin activity (0.4 ng/ml/hr) and low plasma aldosterone level (2 ng/100 ml).

Urinary 11β-hydroxy-steroids were increased relative to 11 oxosteroids (THF: 110, THE 8 µg/day; ratio 13.8. Control ratio 0.4) indicating 11 β-hydroxysteroid-dehydrogenase deficiency. Both parents were normal. The hypertension and hypokalemia were unresponsive to spironolactone. Dexamethason treatment did not influence the hypokalemia and even increased blood pressure. Triamterene (3 x 25 mg) normalised serum potassium, but addition of furosemide (2 x 10 mg) was required for normalisation of blood pressure. This treatment resulted in catch up growth (from -3.6 SD to -1.8 SD for height).

This is the youngest patient known with this syndrome. Unlike the other cases (Ulick et all. J.C.E.M., 49: 757, 1979) he did not respond to triamterene alone. Also the growth retardation and catch up growth after treatment is documented for the first time.