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Late onset 21-hydroxylase deficiency presenting as pre-pubertal gynaecomastia.

Pre-pubertal gynaecomastia has been described in 11β- but not in 21-hydoxylase deficiency. An 8-yr old boy presented with bilateral 5 cm breast buds: P2 G2 Testes 2/2 ml; height 138.5 cm bone age (TW2) 12.5 yrs. Serum hormone levels basally and post-ACTH are shown below. Prolactin was 254 µU/l, DOC 91 pmol/l supine PRA 3.0 ng/ml/hr, SHBG 155 nmol/l. GnRH stimulation at 0' and 20': LH 2.6 and 4.2, FSH 5.4 and 6.3 iu/l. E1 450 pmol/l. Capillary GLC of urine showed typical pattern of 21-OHase defect.

		Basal	+60' post ACTH
T	(nmol/l)	1.1	2.3
A	(nmol/l)	4.0	7.0
DHEAS	(umol/l)	4.4	4.1
E2	(pmol/l)	0.11	0.11
17OHP	(nmol/l)	16.0	177.0

Comparison of DHEAS/E1+E2 and A/E1+E2 gave values comparable to transient pubertal gynaecomastia range for bone age as reported by Moore et al (JCEM 1984 58: 492) and in which peripheral conversion of adrenal androgen to E1 and E2 is suggested as the cause of the condition. It remains unexplained why pre-pubertal gynaecomastia is rare in 21-OHase but not 11β-OHase deficiency.

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HLA and congenital 21-hydroxylase (21-OHD) deficiency : further evidence for a 21-OH locus between DR and GLO.

Congenital adrenal hyperplasia (CAH) due to 21-OHD has been found to be closely linked to the major histocompatibility complex (MHC) and more specifically to HLA-B. A two gene model, one on either side of HLA-D has however been suggested by several authors. We report studies in a CAH family suggesting that the (or one of the two) 21-OH gene might be centromeric to D. The index patient presented ambiguous genitalia (stage III) but no clinical salt loss ; diagnosis was delayed and progressive virilization developped : at 3 yr 4/12, pubic hair, accelerated growth and bone maturation (5 yr). Diagnostic levels (ng/dl) of testosterone (163) and 17α -OH-progesterone (OHP) (basal = 28690 – 114,910 after ACTH) were found. Elevated baseline levels (ng/dl/h) of PRA (1563) further rose after Na restriction (2880) or ACTH (4900). The 3 brothers were clinically normal. HLA typing revealed the first to be heterozygous, the 2nd homozygous normal ; the 3rd was found to be HLA identical and MLC identical to the CAH-sister (A_2CW6 B57 DR6/AW30 CW_2 BW47 DR_2). Microlymphocytotoxicity tests excluded any recombination between the A and D loci. Hormonal studies (baseline and ACTH stimulated levels of OHP, progesterone and cortisol) showed a typical heterozygote response in both the mother and brother n° 3. Unfortunately, studies of the red cell glyoxalase I (GLO) were not informative. However, a DR-GLO recombination is the likely explanation for the present findings, suggesting a 21-OH locus between DR and GLO loci.

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Neonatally elevated 17-OH-progesterone (17-OHP) in so-called late onset congenital adrenal hyperplasia (21-OHase deficiency).

At 23yrs of age a CAH (21-OHase) was diagnosed in a woman complaining of (slight) hirsutism and oligomenorrhea. During dexamethasone treatment she went through 3 normal pregnancies. The first child (boy) had a largely elevated 17-OHP at 2 days of age (280nmol/l) but was left untreated. At age seven he was healthy and had normal height and bone age. The second child (girl) when examined at 4 yrs of age showed no virilization, normal heigth and bone age. Both children then showed elevated basal levels of 17-OHP; 16,5 and 29nmol/l which increased to 147 and 220nmol/l 60'after ACTH (0,25mg iv). The cortisol response to ACTH was poor (205 to 295nmol/l) for the girl and borderline low (215 to 488) for the boy. The third child was healthy in all mentioned respects. The three affected members of the family fell within the range of individuals with acquired or cryptic CAH (M.I.New et al. J.Clin.Endocr. Metab. 57:320 (1983). HLA typing of the family was consistent with the biochemical classification. Conclusions: The present family indicates that even in the so-called late onset or acquired 21-OHase deficiency, the enzymatic defect is present and expressed at birth. If so all children detected in neonatal screening program may not need treatment.

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Elevated Prolactin (PRL) and normal gonadotropin levels in salt-wasting congenital adrenal hyperplasia (SCAH).

Important aims of CAH therapy are normal puberty and gonadal function. To study the hypothalamo-pituitary axis, we applied a combined GnRH/TRH bolus test to 12 patients with SCAH (9 ♀, 3 ♂), age 1.3 to 16.8 yrs, and to a group of 135 age and sex matched normal children (GnRH 60 µg/m², TRH 100 µg/m² i.v.). Plasma LH (IRP 68/40), FSH (IRP 78/549) and PRL (WHO 75/249) were measured by RIA at 0 and 30 min. All except one male CAH pt were medically well controlled as shown by plasma androgens, 17-OHP, PRA, bone age and growth rate. *Results:* All SCAH pts showed normal LH and FSH levels relative to their pubertal stage. PRL in normal children over 2 yrs of age ranged from 2.1 - 14.8 ng/ml (5.5 ± 2.3; $\bar{x}$ ± SD) at time 0 and from 7.3 - 48 ng/ml (26.2 ± 8.9) at 30 min with no difference in sex, age or stage of puberty. SCAH pts showed significantly higher ($P < 0.001$) PRL levels of 7.3 - 24.5 ng/ml (11.4 ± 6.1) at time 0 and of 26.8 - 100 ng/ml (62 ± 24) at 30 min. The highest PRL levels were seen in the postmenarcheal patients. *Conclusion:* Hyperprolactinaemia and hyperandrogenism so far have been reported in patients with hirsutism but not in patients with CAH. Our patients did show hyperprolactinaemia despite normal androgens. Intermittently increased production of androgens, progestins and/or CRF/ACTH might lead to hypothalamic dysfunction and thus to PRL oversecretion.

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Normal ACTH levels in saltlosing congenital adrenal hyperplasia (CAH) with elevated plasma renin concentration (PRC). The effect of mineralocorticoid treatment.

Eleven patients with salt losing CAH (21 OH deficiency), aged 5-19 years were treated with cortisone 20-55 mg/m²/24 h in 3 divided doses and supplementary salt. Normal (< 60 m.i.u./l) and moderately raised (133, 140 m.i.u./l) PRC values in 4 patients were compatible with good control - normal excretion of pregnanetriol (Ptriol). High PRC values (153-522 m.i.u./l) were found in connection with high values of Ptriol (6.5-34.8 µmol/24 h). Plasma Aldosterone (PA) was 3-11 (control values <18) ng/100 ml. Normal ACTH values (11-82 pg/ml) were found in all patients - in one pt. with high PRC (522 m.i.u./l) ACTH was 99 pg/ml.
During maintenance of cortisone therapy, mineralocorticoid (Florinef(R)) was added to the treatment. The dose was gradually increased over a period (median 15 months) up to 1-4 µg/kg/24 h (2 doses) and normal PRC values were established. PA decreased significantly to values below 4 ng/100 ml. Ptriol excretion decreased markedly (to 0.4 -69 µmol/24 h). ACTH values were still in the normal range. During the observation period no change in growth velocity could be demonstrated.

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Pubertal Growth in Congenital Adrenal Hyperplasia.

Diminished final height was noted in cases of CAH due to 21-hydroxylase deficiency. Overdosage of glucocorticoids in infancy and blunted growth spurts in adolescents were assumed to be the causes. - This study focuses on pubertal growth in 26 female CAH-patients adequately treated with gluco- and mineralocorticoids. 17 girls in group I received 20-25 mg/m² of hydrocortisone and if necessary 0,025-0,15 mg of 9α-fluorocortisol. 9 girls in group II received an additional cyproterone-acetate therapy if bone age (BA) advanced height age (HA) for more than 1 year. Group I: A pubertal growth spurt was found in 14 girls (82,4%) with a peak height velocity of 6-2±1,6 (SD) cm/yr. In puberty the BA of early treated girls developed slowly. Based on the BA the peak height velocity was therefore even elevated up to 8,7± 1,4cm/yr. BA.
Group II: Cyproterone-acetate suppressed symptoms of puberty but did not extinguish growth spurt. During 6,3±1,3 yrs. of treatment BA advanced only 4,2±0,7 yrs. However, in this period height increased by 20,8±6,4 cm which corresponds to a mean height velocity of 3,3±0,8 cm/yr., and 4,9±0,8 cm/yr. BA. In 4 patients adult height had improved by 6,5±1,5cm compared to the prognosis of adult height before treatment. In summary, adequately treated CAH-girls showed normal values for pubertal height velocity, those treated additionally with cyproteroneacetate exhibited improved height velocity and adult height.