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HLA and hormonal studies in families of patients with 21-hydroxylase deficiency - cryptic patients?

The study comprises 14 families with unaffected siblings and with one or two children (total 17) with congenital adrenal hyperplasia (CAH)-21 OH defect. HLA tissue typing and glyoxalase (GLO) confirmed the close genetic linkage between 21 OH def. and HLA-B locus. Positive association with B 47 was found: in 2 of 18 unrelated patients (normal population o.4%, $p < o.ol$), negative association to B 8 (only one positive), and no selective increase in B 5 (2/18, normal pop. lo%, NS). HLA genotyping demonstrated 9 heterozygote carriers and 3 normal homozygotes among the siblings. Hormonal analyses showed that basal ACTH values were normal in all relatives and ACTH stimulated values for cortisol and 17 OH-progesterone in the relatives were overlapping with normal values. One family showed: F: A3 B7/A19 B14 - M: A29 B21/A1 B17 - 1) healthy sister: A19 B14/A1 B17, 2) classical CAH patient: A3 B7/A1 B17, 3) late onset patient: A19 B14/A1 B17. B14 was found in the late onset patient, the father and the healthy sister, and these two were from HLA types and hormonal analyses shown to be what is called "cryptic" patients or "unusual heterozygotes".

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Cushing's syndrome secondary to ACTH-secreting Wilms'Tumor.

In a review of the literature we only found one case of Wilms' tumor associated with "ectopic ACTH syndrome". We are reporting the second documented case. A girl, 7 1/2 years old, who 5 months ago presented a sudden gain in apetite and corporal weight. On admission she had the classical cushingoid appearance and a blood pressure of 160/120 mmHg. A large hard mass was palpable in the right side of the abdomen. The urography and renal arteriography demonstrated the presence of a right renal mass. Hormonal assays were consistent with Cushing'syndrome; the serum ACTH levels were extremely high. After surgical removal of the mass, we suspected it to be a stage I Wilms'tumor; this was confirmed through histopathological studies. Chemotherapy was initiated following the protocol of The National Wilms'Tumor Study Group. The girl quickly lost her cushingoid appearance and weight excess. Postoperative serum ACTH levels were normal. In order to explain the ectopic ACTH synthesis mechanism several theories are actually on discussion, such us loss of genetic depressor mechanisms, presence of abnormal DNA, and APUD system.

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CHANGING RESPONSIVENESS OF DHA TO ACTH

In order to evaluate the regulating mechanism of the secretion of DHA, its response to ACTH (Synacten 0,15 mg/m^2 i.v.) was measured in 79 children: 34 with normvariant growth serving as controls (A), 27 with idiopathic hypotituitarism (B), 11 with Turner's Syndrome (C), 7 hypergonadotrophic hypogonad males (D). The children were divided into 3 groups: I.preadrenarche (B.A., 7.5 yrs), II. adrenarche (B.A. 7.5 yrs + no gonadarche), III. gonadarche. The facilatory effects on DHA in terms of peak/basal concentration ratio in the control groups showed that the responsiveness was highest in group AII (N=16, B.A.=10.8) being 2.58 while in groups AI(N=5; B.A. 6.5) and AIII(N=13; B.A.=14.2) ratios were 1.58 and 1.31. The ratios in the groups with hypopituitarism paralleled the normal groups in relation to B.A.: BI(N=5; B.A.=6.6) ratio 1.66; BII(N=9; B.A.=10) ratio 2.26; BIII(N=6; B.A.= 12.3) ratio 1.78. In 7 subjects of this group no response was seen. The ratio was 2.09 in group CII(N=11; B. A.=11.2) and 1.41 in group DNN(N=7; B.A.13.1). The present data - although limited - pose two questions: Does the DHA responsiveness to ACTH peak during the onset of adrenarche? Is this responsiveness more closely associated with bone age(B.A.) than with pubertal development?

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Dexamethasone suppressible hypercorticosteronism in two 46,XX subjects with ambiguous genitalia and ovarian cysts. Partial defect of 17α-hydroxylase or 17-20 lyase?

The paradoxical association of female pseudohermaphroditism and androgen deficiency was observed in two 46,XX subjects with high corticosterone plasma levels. Subject 1 has been declared as a boy due to clitoris enlargement; she had no vagina and uterus. Subject 2 had ambiguous external genitalia. In both, at age 27 and 17 years, were observed fusion of outer labia, impuberism, ovarian cysts, and histologically normal ovarian tissue. Blood pressure was normal. Basal cortisol levels were normal but unresponsive to ACTH. Progesterone levels were 40 and 62 ng/ml and rose after ACTH (50 and 79 ng/ml). 17-hydroxyprogesterone levels were 25 and 21 ng/ml and did not rise after ACTH. Corticosterone levels were 70 and 92 ng/ml and rose after ACTH (110 and 180 ng/ml). All three steroids were suppressed by dexamethasone. Androgen and estrogen levels were at or below the lower limit in normal women. The sex steroid levels were confirmed by mass spectrometry. We suggest that the sexual ambiguousness resulted from an excessive production of gestagenic steroids during fetal life, and that the enzyme defect is either a partial 17α-hydroxylase defect combined with a peripheral production of 17-hydroxyprogesterone, or else a combination of 17-20 lyase defect and a 21-hydroxylase defect limited to the cortisol pathway.

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Progressive adrenal failure in polyglandular autoimmune disease.

We describe here the clinical course of a boy who developed isolated failure of the zona glomerulosa as part of polyglandular autoimmune disease(PAD)and in whom function of the zona fasciculata remains intact. Initially the patient presented with hypoparathyroidism and mucocutaneous candidiasis. ACTH tests at age 8 and 11 yrs resulted in a normal response of both mineralo- and glucocorticoids. The constellation of hyponatremia, hyperkalemia and growth failure at age 14 yrs prompted a reevaluation. A repeat ACTH test, assessing individual contributions of zona fasciculata and glomerulosa, showed normal plasma cortisol, DOC and B responses and a normal urinary response of 18 OH DOC and TH DOC. Urinary 18 OH B and urinary as well as plasma aldosterone were undetectable. Plasma renin activity(PRA)was markedly elevated. The ACTH response of adrenal androgens, presumably metabolic products of the zona reticularis was also deficient. Antiadrenal antibodies against all three layers of the adrenal cortex were positive. Mineralo-corticoid therapy resulted not only in normalization of electrolytes and PRA but also in catch up growth. The course of this patient suggests that in addition to monitoring the electrolyte status, periodic tests for both mineralo- and glucocorticoid synthesis should be performed in children with PAD because progressive adrenal insufficiency may go unrecognized.

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PSEUDOHYPOALDOSTERONISM: SEVERE URINARY SALT-WASTING WITH GENERALISED MINERALOCORTICOID UNRESPONSIVENESS.

Two male infants, each with consanguinous parents, presented with urinary salt-wasting, hyponatraemia and hyperkalaemia aged 8 and 10 days. Plasma renin activity, aldosterone and 17OH-progesterone were elevated, becoming normal after correction of salt-depletion. Urinary tetrahydroaldosterone was elevated on GCMS analysis. No reduction of urinary sodium occurred with fludrocortisone 1.0 and 0.75 g daily. Sweat sodium (179 and 150 mmol/l) and salivary sodium (143 and 154 mmol/l) were elevated. Transmural rectal potential difference was diminished indicating impaired intestinal sodium reabsorption. Peritoneal dialysis was used in one subject to control initial hyperkalaemia (12 mmol/l). Subsequent electrolyte balance was difficult to maintain with hyperkalaemia persisting and episodic hyponatraemia associated with hypertension - possibly related to hyperreninaemia. The clinical condition of the subjects at ages 4 and 6 months was stable on oral sodium intakes of 36 and 48 mmol/kg daily. These features suggest a generalised defect of sodium transport probably due to mineralocorticoid unresponsiveness.