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SOMATOCRININE (GRF) I.V. BOLUS DOES NOT INCREASE SERUM GROWTH HORMONE (GH) IN PATIENTS WITH ACTIVE CUSHING'S DISEASE (CD): RESPONSE RESTORED BY LOWERING SERUM CORTISOL (F) CONCENTRATION.

Low GH response to provocative stimuli in CD is a well established phenomenon. However most of the stimuli used act through release of endogenous GRF and it is not known whether hypercortisolaemia interferes with hypothalamic GRF generation, or GRF action upon somatotrophs, or both. To investigate pituitary GRF responsiveness in hypercortisolaemia we used GRF-44 (Sanofi) as a i.v. bolus (2 µg/kg) in two patients with pituitary dependent CD. Patient AP was a 13½ yr old girl with intermediate lobe type CD present for 6 yr but recognized and treated by bromocriptine for the last two yr. One month after therapy was stopped her midnight F was 17.9 µg/dl; the peak serum GH response to GRF was 3.6 ng/ml and to oral clonidine 0.8 ng/ml. After one month's bromocriptine treatment the midnight serum F concentration decreased to 1.3 µg/dl. Peak GH response to GRF and clonidine at that time were 14.9 and 4.7 ng/ml. Patient AK a 10½ yr old boy with a 4 yr history of anterior lobe CD and midnight serum F level of 33.5 µg/dl, responded to GRF and clonidine tests with GH peak values of 1.0 ng/ml and 0.6 ng/ml respectively. In patient AK the midnight serum F was 39.3 µg/dl after 1 month's of bromocriptine treatment. The GH response to GRF and clonidine were 1.0 ng/ml and 2.6 ng/ml respectively. We conclude that hypercortisolaemia in patients with CD interferes with pituitary responsiveness to GRF; in vitro studies by others suggested this is not a direct effect on the somatotrophs.

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OP'DDD IN CHILDREN WITH MALIGNANT CORTICOSURRENALOMA (MCS)

To design a therapeutic protocol in children with MCS we studied retrospectively a serie of 24 children, 14 boys and 10 girls, aged 6 months to 14 years, with giant secreting tumors (diameter > 10 cm). 3 groups may be considered 1) 8 had surgery and irradiation ; 2) 9 had surgery followed by op'DDD (6-10 g/m^2) ; 3) 7 had op'DDD 10 g/m^2, before (2-9 months) and after (1 to 3 years) surgery. In group 1 all children died a few months after surgery. In group 2, 1 child only is still alive. In group 3 presurgery op'DDD allowed in 6 out 7 cases a marked reduction of the tumor with rapid disappearance of hormonal abnormalities. However no effect was obtained on lung metastasis present in 1 case. In one patient no effects were observed. After surgery and post-surgery op'DDD, 5 of these children are still alive after a delay 1 to 10 years. In conclusion op'DDD appears efficient in many children with malignant corticosurrenaloma when given at high doses (10 g/m^2), prior to surgery for at least 3 months and post-surgery for at least 2 years. The direct effect of op'DDD on tumoral volume appears to be a major factor of the prognosis in children with MCS.

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TRILOSTANE IN THE TREATMENT OF PRIMARY ADRENOCORTICAL MICRONODULAR DYSPLASIA (PAMD)

A rare cause of Cushing's syndrome is a pituitary-independant nodular dysplasia of the adrenal cortex. A 4 year old girl presented with advanced clinical features of Cushing's syndrome. Abdominal CT-scan and adrenal scintigraphy revealed bilateral adrenal hyperplasia whereas a cerebral CT-scan was normal. Serial determinations of plasma ACTH together with dynamic tests using dexamethasone, metyrapone and vasopressin indicated a primary, autonomous, adrenal dysfunction. Treatment with Trilostane - an inhibitor of 3β-hydroxysteroid-dehydrogenase - in a dose of 50 mg t.i.d. was effective, and cortisol excretion was instantly reduced to a low normal level with only a slight increase in ACTH. No side-effects of this treatment were seen and the clinical features of the syndrome regressed. The therapeutic index of Trilostane was small, however. Serum levels of adrenal androgens remain increased therefore a long-term treatment in this young girl was considered to be unfavourable. At laparotomy both adrenals were almost normal in size and a subtotal adrenalectomy was performed. Microscopically, the picture was typical for PAMD with normal structure of the cortex between the micronodules.

Trilostane seem to be effective in improving clinical and some of the biochemical parameters even in a severe case of PAMD but its use may be limited to a short-term preoperative treatment.

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MODE OF INHERITANCE IN PSEUDOHYPOALDOSTERONISM (PHA): AUTOSOMAL RECESSIVE AND DOMINANT TRAIT IN TWO FAMILIES.

We recently described deficient or greatly dimished type I-mineralocorticoid receptors in mononuclear leucocytes of patients with PHA. The clinical features of this syndrome, e.g. insensitivity to mineralocorticoids with renal salt loss leading to hyponatremia and hyperkalemia, can be explained postulating absence of type I-receptors also in the classical target organs for mineralocorticoids. In the first family studied and already reported, an autosomal recessive mode of inheritance had been suggested by normal receptor data, as well as empty history of both parents. Further suggestive of an autosomal recessive trait in this family is the fact that these parents are first degree cousins.

The second kindred studied, however, showed a clear autosomal dominant mode of inheritance. The index case presented with a salt-losing crisis and was shown to have greatly dimished amount of type I-receptors in the mononuclear leucocytes (75 receptors/cell (r/c)). Slightly reduced amount of receptors were found in the mother (95 r/c) and the mother's sister (140 r/c), as compared to the normal range of 150-600 r/c. The first child of this woman had no detectable type I-receptors, but was able to conserve sodium normally.

The different mode of inheritance in these two families suggest that the syndrome of PHA might be the consequence of different defects.

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APPARENT IMPAIRMENT OF ALDOSTERONE SECRETION IN ISOLATED PRIMITIVE GLUCOCORTICOID DEFICIENCY.

9 unrelated children (2 F, 7 M) with glucocorticoid deficiency form adrenal origin were studied. They were 19 days to 8 years at diagnosis. The disease was revealed in 7 cases by hypoglycemia and/or seazures and suspected in the 2 others because achalasia. Sibling from 4 families died suddenly in childhood. Biological findings showed : very low cortisol levels without any response to synacthen. DAH and Δ_4 did not react to synacthen too. Extremely high ACTH levels (x = 1270 (range 328 - 3095), N = < 90 pg/ml) ; low basal aldosterone values (x = 16.4, range < 10-31, N = 10-60 pg/ml) with an impaired response to synacthen (x = 27.2, range < 10-80, N = 60-310 pg/ml) as observed in complete adrenal failure. But evidence for intact mineralocorticoid function was provided by following date : 1) renin activity in each patient was in the normal range for age before and on exclusive glucocorticoid treatment (4 years 1/2 follow up) ; 2) Salt deprivation (.3 mEq/kg/5 days) performed in 5 cases was well tolerated and accompanied by a rise in renin and aldosterone levels (mean 5 and 12 fold respectively) ; 3) when in 4 cases DXM (2 mg/m^{2}73 x 48 h), succeded in lowering ACTH level to the normal range, then a significant response of aldosterone to the synacthen test was observed in 3 (reaching 102, 134 and 215 pg/ml) contrasting with the absence of any rise in androgen levels. These findings may suggest that a large amount of endogenous ACTH was occupying all the receptors sites of the intact zone glomerulosa, while the fasciculata-reticularis remains unresponsive to ACTH.

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FAMILIAL ADRENAL FEMINIZATION PROBABLY DUE TO INCREASED STEROID AROMATIZATION

5 of 10 members of a non-related North African family(father, 2 male,2 female siblings) were observed or reported to have had gynecomastia,early growth spurt for chronologic age(CA),and short final stature. The extensively studied 8 year old propositus had advanced bone age (BA,13 yrs) and height 135.6cm (normal for CA (+1.1SD), short for BA(-2.5SD)). He presented with facial acne, gynecomastia (B3), pubic hair (Tanner 2), and testicular volume 2ml. Blood pressure was normal (90/70 mmHg). Urinary total 17-KS (2.1mg/d),17-OHC(2.4mg/d),and individual steroids (gas chromatography) were normal.Cortisol,S,and 17OHP in plasma responded normally to ACTH. Basal estrone (E1,181 pg/ml) was elevated, and increased with ACTH (223 pg/ml). After hCG, testosterone(T) responded normally(55 to 164ng/dl),but neither E1(135 to 139pg/ml),nor estradiol(E2,86 to 85 pg/ml) did increase.The assumption of ACTH-dependent adrenal feminization was confirmed by a reduction of breast tissue with dexamethasone or cyproterone acetate treatment. However, this effect was only transient. Subsequent testolactone treatment (450 mg/d) resulted in an increase of the T/E2 (5.6 to 20.3),and A/E1(3.4 to 31.4) ratios, and in reduction of breast tissue. It is concluded that this is a familial type of non-tumorous adrenal feminization with increased adrenal androgen aromatization for unknown reasons.