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BODY PROPORTIONS IN CONGENITAL ADRENAL HYPERPLASIA (CAH).

It has been proposed that testosterone-induced growth produces a disproportionate increase in trunk length. Since there is increased adrenal androgens in CAH from early fetal life which may continue intermittently postnatally, disproportionate growth might be expected. Body proportions were measured in 27 CAH patients (19F, 8M; 3 late-onset) aged 4-21 yr (CA) who had been treated with hydrocortisone 15-20 mg/m^2/day in infancy and childhood, and dexamethasone 0.25 - 0.75 mg/day in later life. Bone age (BA) determined by the TW2 method was in advance of CA in all but one patient. Statural growth was complete in 9. Standard deviation scores (SDS) were calculated for sitting height (SH) and sub-ischial leg length (SLL). SH (SDS) and SLL (SDS) for CA were -0.47 $\pm$ 1.44 (mean $\pm$ SD) and -0.49 $\pm$ 1.10, respectively; when related to BA the scores were more negative (-1.32 $\pm$ 1.28 and -1.1 $\pm$ 1.19, respectively). The difference between the scores (SH (SDS) - SLL (SDS), equivalent to 0 in perfect proportion) was 0.01 $\pm$ 0.95 indicating normal body proportions. The exception was an untreated, late-onset girl whose SDS difference was +2.1, indicating disproportionate trunk growth. When stature is below normal in CAH, it is generally proportionate. Androgen-induced disproportionate growth only arises postnatally and after chronic androgen excess.

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GROWTH RETARDATION IN CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA (CAH) WITH PREDNISONE SUBSTITUTION IS NOT GROWTH HORMONE (GH) AND IGF 1 DEPENDENT

Prednisone inhibits growth more potently than hydrocortisone. Supression of GH secretion has been discussed as one possible mechanism. In a retrospective study GH, IGF 1 and procollagen type III propeptide (P-III-NP and FAB), which correlates to growth velocity , were determined longitudinally in sera of 9 children with CAH (age: 6 to 11 ys) during an intermittent period of prednisone substitution (4mg/m^2/bid) for 6 to 24 months and a subsequent period of hydrocortisone substitution (20mg/m^2/tid) for 24 months. Prednisone treatment led to a deceleration of mean growth velocity (0.5 to -4.7 SDS for bone age) without delay of sceletal maturation resulting in a mean decrease of final height prediction of 6 cm. While IGF 1 (4.7 $\pm$ 2.1 vs. 4.3 $\pm$ 1.2 U/ml, mean $\pm$ 1 SD) and GH (5.6 $\pm$ 6.1 vs. 4.0 $\pm$ 6.9 ng/ml) did not differ during both periods, P-III-NP (13.1 $\pm$ 3.5 vs. 28.6 $\pm$ 7.4 ng/ml) and FAB levels (63 $\pm$ 18 vs. 128 $\pm$ 29 ng/ml) were reduced ($p<0.001$) during prednisone substitution. During both regimens in 2 of these children the nocturnal GH secretion (above 2500 ng$\cdot$min$\cdot$ml^{-1}), stimulated GH levels after insulin-induced hypoglycaemia (above 15 ng/ml) and after GRF administration (above 25 ng/ml) were normal. Our observation gives strong evidence that the impairment of growth by hydocortisone-equivalent doses of prednisone is not mediated by changes of GH and IGF1 secretion but rather by a peripheral inhibition of GH and IGF1 effects at the tissue level.

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URINARY EXCRETION OF TETRAHYDROALDOSTERONE IN NEWBORNS WITH SALT-WASTING 21-HYDROXYLASE DEFICIENCY.

Tetrahydroaldosterone (3α, 5β) is excreted in urine as glucuronide and is the major known metabolite of aldosterone. Estimation of this parameter gives a valuable information on diurnal aldosterone production compared to a single estimation, of plasma aldosterone concentration.

Urine samples collected during hospitalization for steroid profiling from 25 untreated newborns suspected of and proven to have salt-wasting 21-hydroxylase deficiency (CAH) were analyzed for Tetrahydroaldosterone 3α, 5β -glucuronide (THALDO). The children were from 1 day to 4 months old, 12 were females, 13 males. The females were all virilized and the boys were either admitted to hospital due to salt-wasting crisis or sibship to children with 21-hydroxylase deficiency (3 cases). In the lowest age group with CAH 1 day - 8 days old, THALDO excretion was 0,2-7 μg/day (mean 1,31 $\pm$ 1,8 μg, n=13) compared to 4-223 μg/day (mean 77 $\pm$ 72 μg, n=24) in normal newborns. In the CAH-group 14 days-1 month the excretion was 0,8-5 μg/day (mean 2,7 $\pm$ 1,3 μg, n=10) compared to 11-29 μg (mean 20 $\pm$ 8 μg, n= 6) in the controls. Two children with CAH, 2 and 4 month old excreted 4 and 5 μg THALDO compared to 2-24 μg (mean 13 $\pm$ 9 μg, n=5) in normals.

In conclusion all 25 children with untreated salt-wasting 21-hydroxylase deficiency had very low aldosterone production irrespective of age. In the normal controls the wellknown increased activity in aldosterone production during the first week of life was demonstrated.

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INTEGRATED CONCENTRATION OF PLASMA CORTISOL LEVEL IN ASTHMATIC CHILDREN TREATED WITH LONG TERM INHALED STEROIDS.

To assess the effect of long term therapy with inhaled beclomethasone dipropionate (BDP) on the pituitary-adrenal axis we measured the integrate concentration of plasma cortisol level (ICPCL) in 8 asthmatic children (aged 6-16 yrs) who received BDP doses of 200-600 /ug/d for 6-48 mos. Controls were 4 children (aged 6-16 yrs) whose ICPCL measured for other reasons were normal. All patients did not receive any oral steroids during the 3 months prior to the study. The ICPCL was determined using a portable withdrawal pump to enable continuous blood specimen collection (every 1/2h) for 24 h. mean ICPCL. Mean ICPCL of the asthmatic children on long term BDP therapy was significantly low (4.9+3.3 /ug%, mean+S.D.) as compared to the healthy controls (8.7+2 /ug%)($p<0.05$, Mann-Whitney U-test). In 5/8 asthmatics the ICPCL was lower than the mean -2SD of the controls: 1.6;2.8;3.1; 3.6;3.8 /ug%. Response of cortisol secretion to IV administration of 0.25 mg ACTH was abnormal in two of the five asthmatic children with low ICPCL. No correlation was found between ICPCL and severity of the asthma, height percentile and the tunner stage.

We conclude that long term therapy with inhaled BDP may cause reduction in the normal physiological secretion of cortisol even with relatively low doses. This effect is probably due to partial depression of the pituitary-adrenal axis.

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GROWTH DURING ALTERNATE-DAY STEROID THERAPY: NEAR NORMAL GROWTH ON STEROID FREE DAYS

Bone growth in rabbits treated with hydrocortisone was measured by Roentgen Stereophotogrammetric Analysis, RSA, which allows very accurate measurements of distance between metallic markers in long bones.

Cortisone was given in im injections as single and as repeated doses, daily or every other day. Single injections of cortisone showed three types of growth influence. Low dose (<4 mg/kg Body Weight,BW) resulted in no growth inhibition. Intermediate dose (4-32 mg/kg) inhibited growth during the first but not the second day after the injection. The inhibitory effect of High dose (64-128 mg/kg) lasted for two days.

During daily treatment growth decreased to a constant level. During alternate-day injections, ADST, with double dose every other day, growth was nearly normalized during the steroid free days. We suggest that ADST has no unfavorable influence on growth if the interval between the injections is longer than the duration of the growth effect of each single dose.

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AGE-RELATED DIFFERENCES IN THE EXCRETION OF DELTA 5 STEROIDS (D5S) IN TWO RELATED GIRLS WITH 3b-HYDROXY STEROID DEHYDROGENASE DEFICIENCY (3bOHD)

2 related females with 3bOHD from the same village in Eastern Switzerland were studied. Pt.1 is a 25 year old adult,whose earlier findings have been reported (Zachmann et al.,J.clin.Endocr. Metab.30,719,1970),pt.2 6 wks old. The mother of pt.1 is a first cousin of the maternal grandmother of pt.2. The relation of the fathers could not be established,but they originate from related local families. Urinary steroids were estimated by gas chromatography on a glass capillary column, their identity was confirmed by mass spectrometry. In pt.1, the main D5S were D5pregnenetriol (110 umol/l),17OH-pregnenolone (6.0),and DHEA (5.6). For reasons discussed earlier,there were also large quantities of hepatic 3a- and 3b-pregnanetriol (114.9). Pt.2 excreted less D5pregnenetriol (12.6 umol/l), but large quantities of more unusual D5S such as 16OH-pregnenolone (14.4), 16OH-DHEA syn (159.5) and anti (101.5), 16keto-D5androstenediol(66.5), 3,16,17-D5androstenetriol (33.1), D5pregnene-3,15,17-triol-20-one(29.2),16OH-pregnenolone (113.8), D5pregnene-3,15,17,20-tetrol(78.6), and 21OH-pregnenolone(18.4). It is concluded that urinary steroids of newborns with 3bOHD are modified considerably by the 16-hydroxylating activity of the fetal adrenals and that they differ from those of older children or adults with genetically the same defect. Without specific steroid analyses, this may cause diagnostic difficulties.

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