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SOMATOMEDINS AND GROWTH HORMONE (GH) SECRETION IN ULLRICH-TURNER SYNDROME (UTS)

In recent time attempts are made to treat short stature in UTS with GH. What evidence exists for a disturbance of the GH-somatomedin axis causing the growth disorder in UTS ? -- In a total of 56 children and adolescents with UTS (45,X;N=45) the following parameters were measured in a cross-sectional manner: somatomedin activity (Sm; porc.cart.), Sm-C/IGF I (RIA), IGF II (RIA),- GH in response to: arginine, GRF(1-29)NH2, and 5.5 h of sleep (SrGH). -- Normal levels of IGF II and to arginin and GRF were seen. Sm was high before BA 10 yrs., normal later. Sm-C was normal before BA 10 yrs, low-normal later. In relation to height Sm-C levels are higher than normal before BA 10 yrs.. SrGH was declining with age not showing the normal puberty-associated rise. Low doses of estrogens (EE, 100 ng/kg d) and oxandrolone (150 ug/kg d) induced a rise in Sm-C. -- The data provide no evidence for the existence of a genuine disorder of the GH-somatomedin axis. They rather point to a partial resistance to this system, at least before the effects of gonadal dysgenesis emerge. Thus, only supra-substitution doses of GH should be effective in improving growth in UTS.

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24 HOUR GROWTH HORMONE PROFILES IN TURNER SYNDROME AND THE EFFECTS OF OXANDROLONE.

Physiological growth hormone (GH) secretion has been assessed by intermittent 20 minute sampling over 24 hours in 31 Turner Syndrome (TS) patients aged 4.3 to 12.4 years. Computer pulse analysis was performed (Merriam & Wachter) and results expressed as the sum of GH pulse amplitudes (SPA).

In 22 profiles the GH pulse frequency was comparable to that seen in normal short children; in 9, the GH pulse frequency was unusually fast (n=7) or showed a single high pulse (n=2). Patterns such as these are associated with low height velocity in short children but the growth of these 9 TS patients was not slower than that of the 22. In the 'normal' profiles there was a decline in SPA with age; this contrasted with IGF-1 concentrations which rose with age. The relationship between height velocity and GH SPA demonstrated in short children (ESPE, 1986) was absent in TS patients.

Oxandrolone given in a dose of 0.9-1.8mg/m^2/24 hours to 12 patients. Height velocity increased; GH profiles did not change but plasma IGF-1 concentrations rose.

We conclude 1) that end organ insensitivity probably plays an important part in the growth failure of Turner Syndrome and 2) that the growth promoting effects of oxandrolone are not mediated by increased GH secretion.

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GROWTH IN THE NOONAN SYNDROME (NS)

The Noonan S. diplays a variety of symptoms similar to the Ullrich-Turner S. (UTS). Main differences to the UTS are (besides some variance in the pattern of dysmorphic symptoms) frequent mental impairments, congenital pulmonary stenoses, absence of gonadal dysgenesis, normal karyotype and occurrence in both genders. Although NS is reported to be more frequent than UTS (1:1000 vs. 1:5000 births) comparatively little is known about its auxology. - Auxolgical data of 80 (45m/35f) cases were analysed and standards for height were derived. NS shows the following auxological characteristics: normal size at birth, - growth at 3rd perc. until puberty, - males are always relatively smaller than females (ca. 1 SD), - puberty is retarded by ca. two years, - height/weight ratio is normal, - BA is retarded, - males (N=12) approach 159.4 (+-6.9) cm, females (N=22) 150.2 (+-9.5) cm. - Female growth differs from UTS also before puberty. -- The data may serve for councelling and may guide during treatment trials with growth promoting pharmaca

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BONE MINERAL CONTENT IN TURNER'S SYNDROME.

Bone mineral content of subjects with Turner's syndrome has been found smaller than predicted by age and sex. Bone mineral content related to bone width (BMC/BW) of 19 patients with Turner's syndrome not yet receiving estrogen replacement therapy (mean age: 11 yrs;range: 6-15 yrs) and of 22 patients receiving exogenous estrogens (mean age: 17 yrs 7/12; range: 11 yrs 8/12-28 yrs 4/12) was evaluated by single photon absorptiometry of distal forearm. In both groups BMC/BW was significantly reduced ($p < 0.025$ and $p < 0.0001$ respectively)when compared with normal subjects. Seven patients with Turner's syndrome,in whom estrogen replacement therapy had begun at a chronological age less than 14 yrs,have been examined longitudinally to evaluate the role of estrogens in bone mineralization. The average increase in BMC/BW was 11% and 7% at 6 and 18 months respectively,after the beginning of therapy. However,the BMC/BW values remained below normal. Our data confirm a deficit in bone mass in patients with Turner's syndrome; bone demineralization is present also at prepubertal age. In our experience,precocious estrogen treatment (11-14 yrs) can improve bone mass in patients with Turner's syndrome.

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EFFECT OF ESTROGEN-PROGESTOGEN TREATMENT ON CARBOHYDRATE TOLERANCE IN TURNER'S SYNDROME

Glucose tolerance was evaluated by means of an OGTT in 16 girls with Turner's syndrome submitted to estrogen-progestogen treatment (10 subjects 45,X, 1 X-mosaic and 5 X structural abnormalities). OGTT was performed before treatment, on treatment after the first 3 months (1st control) and after various cycles of 3 months each (2nd control), and after therapy withdrawal for 3 months after last cycle. On treatment: significantly higher blood glucose values than those of pretreatment were present at the 1st control at time 90 ($p < 0.01$) and 180 mins ($p < 0.025$) and for the area ($p < 0.005$) and at the 2nd control at time 90 ($p < 0.01$), 120 and 180 mins. ($p < 0.025$) and for the area ($p < 0.05$). Insulin values were significantly higher than those of pretreatment OGTT at time 180 ($p < 0.05$) for the 1st control and at time 90 ($p < 0.01$) and 180 mins and for the area ($p < 0.05$) at the 2nd control. After suspension of treatment: Blood glucose and insulin values were lower ($p < 0.05$ at 180 mins) than those observed during treatment and no longer showed significant differences compared to pretreatment values. These data show estrogen-progestogen replacement therapy induces an increase in insulin requirements which however does not prevent an increase in blood glucose values. This phenomenon can be reversed after hormone replacement treatment has been suspended. In conclusion although care should be exercised when Turner's patients receive steroid replacement therapy, brief treatment withdrawal seems sufficient to induce a recovery of glucose tolerance.

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THE EFFECT OF SHORT TERM HIGH DOSE TESTOSTERONE THERAPY ON BONE AGE (BA) AND HEIGHT IN TALL BOYS

We have prospectively evaluated the effect of a short term high dose testosterone therapy on height and BA in tall boys. BA was assessed according to the Greulich-Pyle method. Adult height was predicted with the tables of Bayley-Pinneau. Treatment consisted of intramuscular injections of 500 mg testosterone oenanthate every 2 weeks for 6 months. Height and BA were determined before, at the end of and 3, 6 and 12 months after therapy.
34 boys have been followed for at least 6 months after therapy. $\Delta BA/\Delta CA$ accelerated by 2.46 ± 0.82 years (mean ± SD) during therapy and by 2.99 ± 1.14, 2.23 ± 0.78 and 1.58 ± 0.46 years 3, 6 and 12 months thereafter, thus demonstrating, that BA-acceleration persists for several months after treatment.
12 boys were measured 2.50 ± 0.34 years after therapy. Their initial bone age was 14.02 ± 0.52 years with a predicted height of 204.99 ± 4.25 cm. At the end of therapy height was 193.61 ± 5.59 cm and bone age 15.67 ± 0.58 years. Height at the time of the last evaluation was 197.38 ± 4.11 cm, which is 7.61 ± 5.6 cm less than predicted. The reduction of 50.26 ± 14.55 % is similar to the one observed in 115 boys treated for 14.25 ± 4.14 months with the same therapeutic regimen.
We conclude, that with the persistent acceleration of BA after treatment only 6 months of high dose testosterone therapy are needed to effectively reduce height in boys with tall stature.