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TESTOSTERONE THERAPY IN BOYS WITH DELAYED PUBERTY

Delayed puberty, often associated with short stature is a common problem in the paediatric clinic.These boys' retarded growth and sexual development causes considerable distress during adolescence.Because testosterone is widely believed to accelerate bone maturation disproportionately and thus reduce final height this treatment is often withheld.

36 boys, aged 12.0-17.7 (mean 14.8) yrs, were treated with testosterone oenanthate 125mg intramuscularly for 3 months.They were seen half yearly and heights (Harpenden stadiometer), skeletal maturation (Tanner RUS (TW2)) and pubertal status (Tanner and Whitehouse) were measured.

At 6 months there was a distinct advance in pubertal status and an increase in height velocity from 4.4 to 9.8cm/year.The boys' morale and confidence increased impressively.No serious side-effects were seen.The effects of treatment on height prediction and height standard deviation score for bone age are shown below:

	Baseline	.5 yr	1 yr	1.5-2 yr
Ht SDS BA	-.91	-.1.18**	-1.02*	-1.09
Ht Pred	166.7	166.5*	167.3*	167.6
No.	36	30	18	8

** =p .05 * = NS Compared with baseline

Treatment with testosterone effectively alleviates the main problems of delayed puberty and our data suggest that at this dosage it has no significant effect on final height.

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LOW DOSE OXANDROLONE THERAPY IN CONSTITUTIONALLY DELAYED GROWTH.

27 boys (aged 7.6-16yrs) with delayed growth were subdivided by testicular size into prepubertal (<4mls) and pubertal (≥4mls). 13 received 2.5mg/d oxandrolone (Ox) for 3 months, and 14 acted as controls. Each group grew at a velocity below the 25th centile over the preceding 0.3-1.4yrs. The controls continued to grow poorly over the next 6 months. Ox promoted an increase in velocity in prepubertal (4.4 to 7.5cm/yr, p=0.05) and pubertal boys (4.7 to 8cm/yr, p<0.05) during therapy, maintained over the subsequent 3 months only in the pubertal group (to 9.3cm/yr). The prepubertal decelerated after treatment (to 5.4cm/yr).

GH secretion (arginine, GRF and during the first 90mins of sleep) was assessed at entry and 6 months in prepubertal controls, and at entry, 3 and 6 months in treated boys. No change in peak GH response or "areas under curve" (AUC) were seen in the prepubertal groups. At 3 and 6 months, treated pubertal boys had significantly greater AUC and GH peaks during sleep than the prepubertal, associated at 6 months with increases in basal testosterone (3.7nmol/l at entry to 18.2nmol/l, p<0.01) and somatomedin-C (140 to 214ng/ml, p<0.05). These changes were not seen in the prepubertal boys.

Ox does not alter the GH status of prepubertal boys, but enhances growth probably through a direct action on cartilage. Persistent growth acceleration in the pubertal boy is associated with increased GH and somatomedin levels.

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TREATMENT WITH CLONIDINE IN SUBJECTS WITH CONSTITUTIONAL GROWTH DELAY (CGD): A CONTROLLED DOUBLE-BLIND STUDY.

In 1985, Pintor et al. reported that treatment with clonidine (Cl), an α2-adrenergic agonist, accelerates growth in children with growth disorders. In order to confirm or disprove this observation, we studied again the effect of Cl in subjects with constitutional growth delay by carrying out a controlled double-blind study. 10 prepubertal patients with chronological age between 7 4/12 and 11 7/12 years and with height < 3rd centile and with CGD were selected. Parents consented to the trial and the patients, after 6 months' observation, were randomly and blindy allocated to Cl (n.5-group 1) or placebo (n.5-group 2) therapy. Cl was administered at a dose of 0.100 mg.m2/die. After a weeks' treatment, a patient from group 2 withdrew from treatment due to sleepiness. The patients were measured 6 months before treatment, at the start, after 6 month of treatment and 6 month after the end of treatment. The height velocity of group 1 children was 4.14, 5.76 and 2.88 cm/year respectively before, during and after the 6 months of treatment, while in group 2 height velocity was respectively 4.70, 5.45 and 3.35 cm/year. The difference in height velocity before and during therapy is significant ($p < 0.05$) only in group 1. There is no difference in height velocity between the two groups before, during and after treatment. GH peak and area in the arginine test and SmC levels are similar in the two groups both before and after treatment. It may be concluded that further, wider double-blind studies are necessary to clarify and quantify the effect of Cl on growth.

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CLONIDINE TREATMENT IN CHILDREN WITH CONSTITUTIONAL GROWTH DELAY (CGD).

Ten children (9 males and 1 female; mean age 9.6 yrs)were treated with clonidide (75 $\mu g/m^2$ p.os b.i.d.) for a period of 6 months. CGD diagnosis was based on the following clinical and laboratory criteria: heigth < 3rd percentile; growth velocity (GV) ≤ 5 cm/yr (4.17±0.2$\bar{X}$± SEM); delayed bone age (BA) by 1 or more yrs and always below the age of 11; Tanner stage I;normal (> 8 ng/ml)peak serum GH responses to clonidine p.os (26±6 ng/ml) and insulin i.v.(III)(14±2.0 ng/ml); somatomedin C (SmC) levels in the normal prepubertal range (0.78±0.13 U/ml).The above mentioned parameters, in additions to OGTT and baseline cortisol (C), I_4 and FT_4 blood levels were examined before and after (exept ITT) 6 months of therapy. During the treatment period mean growth velocity increased ($p < 0.01$) from 4.2± 0.2 to 5.3±0.3 cm/yr although only 3/10 subjects showed a 50% increment compared to pre-therapy values. GH peak values after clonidine (30.9±5.8 ng/ml),glucose levels in response to OGTT and baseline SmC, and thyroid hormone levels did not change after therapy. No significant correlation was found between GV after therapy and GH responses to provocative tests, GV, BA and chronological age before therapy in any patient. No important side effects were recorded. In conclusion, these preliminary results indicate that clonidine might be effective in enhancing GV of some children with CGD although we were not able to differentiate responders from non responders based on clinical and laboratory parameters.

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PHYSIOLOGICAL GH SECRETION IN CHILDREN WITH SHORT STATURE DUE TO LOW BIRTHWEIGHT/RUSSELL-SILVER SYNDROME.

We have studied 24 prepubertal children (7F,17M) with short stature, mean height SDS -2.8 (range, -5.2 to -1.7) as a consequence of intrauterine growth retardation. Mean age at assessment was 6.3 yrs (range, 1.6-9.6). Mean birthweight SDS, allowing for gestational age, was -2.9 (range, -5.0 to -2.0). Mean height velocity SDS was -0.9 (range, -2.6 to + 1.0). Mean bone age delay was 0.6 "yrs". Patients were divided into 2 groups; 11(3F,8M) had dysmorphic features of the Russell-Silver syndrome (RSS group) and 13 (4F,9M) did not (non RSS group).

All children had an overnight serum GH profile from 1900-0800 hrs via an indwelling intravenous cannula with blood drawn at 15 minute intervals. A PULSAR computer programme was used for GH pulse analysis. GH pulse frequency, area under the GH pulses and sum of the GH peaks were calculated. All children had a maximum GH peak >20 mU/l except one boy who only attained a peak GH of 14mU/l. One boy in the non RSS group had high frequency "neurosecretory dysfunction". The most pronounced abnormality in 6 of the 11 children with RSS was that only one large GH pulse during the night was observed with a mean value of 37 mU/l (range, 27-65). GH secretion remained detectable between pulses in 6 of the children in the non RSS group.

It is probable that more than one endogenous GH pulse during the night is required for normal growth. Although growth failure in RSS is multifactoral and end-organ insensitivity is probably important, abnormal GH secretion may be contributory.

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FINAL HEIGHT (F.H.) IN A GROUP OF CHILDREN WITH CONSTITUTIONAL GROWTH DELAY (CGD)

On the basis of recent evidences, CGD seems to be a heterogeneous disorder and it has been hypothesized that some of these children could profit from different therapies.We investigated the natural outcome of a group of never treated CGD children especially in regard to their F.H..49 children (35 males and 14 females) with CGD have been followed at least yearly since prepuberty till the end of growth (bone age > 18 yrs in f.and > 19 yrs in m.).At diagnosis height was between -1 and -3 standard deviation score (SDS)(20% of the patients < 2.5 HSDS); bone age (BA)at least < 2DS for chronological age (CA)and growth velocity in the low-normal range for CA.The most important results can be summarized as follows: -mean F.H. was reached later than in normal population (17-23 yrs CA);it is always in the normal range and well correlated with the genetic target calculated on the basis of parental height (=0.68; p < 0.001).Just in 1 case F.H.was < -2DS from the target.-Height prediction (Bayley and Pinneau) is correlated with F.H. both in prepuberty and in puberty ($p < 0.005$);however it overestimated in both age groups (31% of cases in prepuberty and 26% in puberty)-Puberty started at 12.4 yrs in f.and 13 yrs in m.and ended 3 yrs later in both sexes.
In conclusion, our data confirm the fact that CGD (at least when prepubertal height is > -3DS) is a benign condition reaching all the patients normal height well correlated with the genetic target.