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Effect of low-dose testosterone treatment on craniofacial growth in boys with delayed puberty

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SUMMARY Craniofacial growth was investigated in boys treated with low-dose testosterone for delayed puberty (>14 years old; testicular volume < 4 ml; n = 7) and compared with controls (12–14 years; n = 37). Cephalometric radiographs, statural height and pubertal stage were recorded at the start of the study and after 1 year. Craniofacial growth was assessed by nine linear measurements.

At the beginning of the study, statural height, mandibular ramus length, upper anterior face height, and total cranial base length were significantly shorter in the delayed puberty boys than in the controls. After 1 year, the growth rate of the statural height, total mandibular length, ramus length, and upper and total anterior face height was significantly higher in the treated boys than in the untreated height-matched controls (n = 7). The craniofacial measurements were similar in the treated boys as compared with the controls.

These results show that statural height and craniofacial dimensions are low in boys with delayed puberty. Low doses of testosterone accelerate statural and craniofacial growth, particularly in the delayed components, thus leading towards a normalization of facial dimensions.

Introduction

The age of onset of puberty varies greatly among normal adolescents, with 95 per cent of boys entering puberty between 9.2 and 13.8 years of age (Tanner, 1978). Although some boys with delayed onset of puberty (beyond 14 years) have some pathology, most of them present a variant of normal development referred to as 'delayed puberty'. These adolescents have a stature that is relatively small for their chronological age, but generally appropriate for their bone age (Stanhope *et al.*, 1985). Despite the perspective of normal adult height, a significant proportion of this group have psychological difficulties relating to their sexual immaturity and short stature (Kulin and Müller, 1996). Because of these problems, together with their decreased bone density (Finkelstein *et al.*, 1992), some of these boys are treated with exogenous androgens (Wilson *et al.*, 1988). The effects of these interventions on statural height and sexual maturity have been examined and are well documented (Rosenfield, 1990; Bourguignon, 1993; Brown *et al.*, 1995).

However, the effects of this treatment on the craniofacial development in boys with a constitutional delay of growth and puberty (CDGP) have not been studied. An association between craniofacial growth and somatic development has been established in longitudinal growth studies (Nanda, 1955; Björk and Helm, 1967; Baughan *et al.*, 1979), and, more specifically, some investigations have shown a relationship between the craniofacial growth spurt and the peak height velocity in body length (Grave, 1973; Thompson and Popovich, 1973; Baughan *et al.*, 1979; Fishman, 1982). Effects of testosterone on long bone growth have been demonstrated (Schoutens *et al.*, 1984; Jansson *et al.*, 1985; Turner *et al.*, 1989). Advanced dental and craniofacial development has been observed in boys with precocious puberty and congenital adrenal hyperplasia (Garn

et al., 1965; Keller *et al.*, 1970; Spiegel *et al.*, 1971). Anabolic steroids, for example, have been reported to modify the normal craniofacial growth pattern in rats (Barett and Harris, 1993).

Estimating the importance of testosterone during craniofacial growth is essential to guide orthodontic treatment decisions and to evaluate treatment results. Therefore, a longitudinal cephalometric clinical study was started over a 1-year period in CDGP boys treated with low-dose testosterone, and in normal healthy control boys in different stages of normal pubertal development. It was the purpose of this study to compare the craniofacial growth of CDGP boys before, during and after their testosterone treatment with that of control boys.

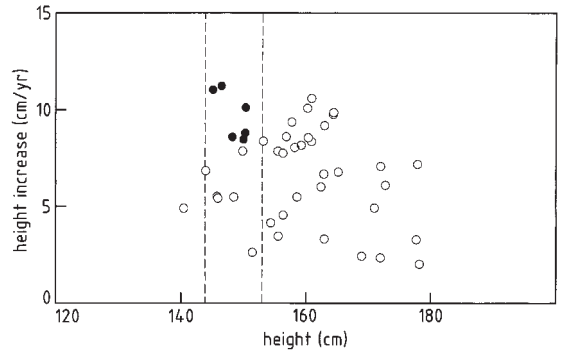

Figure 1 Increase in statural height after 1 year as a function of height at the start of the study, for controls (○; $n = 37$) and delayed-puberty boys (●; $n = 6$). The vertical lines indicate the margins for selection of the height-matched controls.

Study population, materials and methods

Study group

The study group initially consisted of seven boys aged between 14.6 and 16.2 years with delayed puberty who were referred to the Growth Clinic of the Department of Pediatrics, Faculty of Medicine, Katholieke Universiteit Leuven, Leuven, Belgium. All were diagnosed as having delayed puberty: testicular volume was <4 ml, statural height was below the third percentile for chronological age, and bone age was between 9.7–12.5 years by the Tanner-Whitehouse II method (Tanner *et al.*, 1983). The treatment consisted of 25 mg of testosterone propionate, twice a month intramuscularly for a 6-month period. One boy was subsequently excluded from the study as he received treatment only for a 3-month period. All subjects had a skeletal Angle Class I relationship with no history of orthodontic treatment.

Control group

The control group comprised 37 healthy boys aged between 12.0 and 14.0 years who were examined at the High School Medical Centre. They were used to compare the distribution of the values of the different parameters of the study group with those of normal boys, both at the start of the study and after 1 year. These control boys were all at different stages of pubertal development.

From this control group, boys in the same (early or pre-) pubertal development stage as the patients of the study group were selected. The statural height at the start of the study was used as criterion for pubertal development stage. This resulted in the formation of the height-matched control group ($n = 7$; Figure 1). The relationship between pubertal stage and statural height was confirmed by their genitalia stage (G-stage). This was G1–G2 at the start of the study, indicating they were only in the first stages of puberty, while their testicular volume at the end of the study was more than 10 ml, indicating they had entered puberty.

Records

At the start of the study and after 1 year, statural height was measured, testicular volume was assessed with a Prader orchidometer (Prader, 1975) and standardized lateral cephalograms, with the subject's head positioned in a cephalostat and orientated to the Frankfort horizontal plane, were obtained.

Cephalometric technique

Cephalograms were traced and seven landmarks were identified (Figure 2). These landmarks were

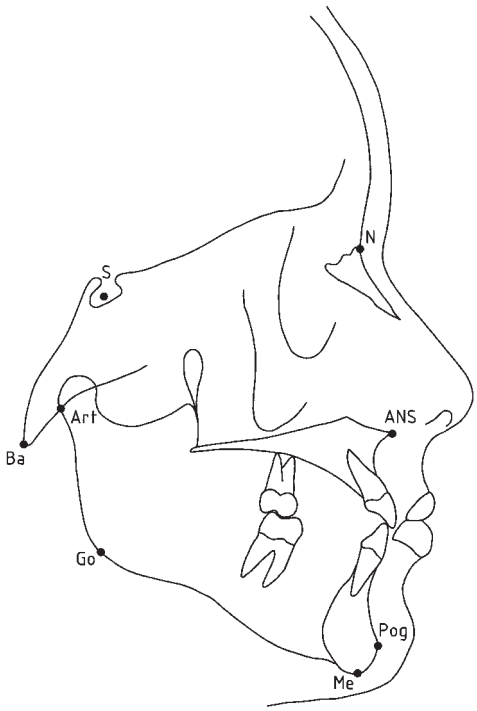

Figure 2 The reference points and measurements on the cephalograms. Nasion–sella: anterior cranial base (N–S); sella–basion: posterior cranial base (S–Ba); nasion–basion: total cranial base (N–Ba); articulare–gonion: ramus length of mandible (Art–Go); gonion–pogonion: mandibular body (Go–Pog); articulare–pogonion: total length of mandible (Art–Pog); nasion–ans: upper anterior facial height (N–ANS); ans–pogonion: lower anterior facial height (ANS–Me); nasion–pogonion: total anterior facial height (N–Me).

digitized and nine linear measurements were computed with the Quick Ceph™ program (Orthodontic Processing, Chula Vista, California, 1993). Replicate analyses showed no significant differences between the intra- and inter-observer measurements.

Linear measurements focused (i) on mandibular growth since it is that part of the face which, in relative terms, continues to grow to a clinically significant degree during puberty (Bishara *et al.*, 1981; Silveira *et al.*, 1992); (ii) on vertical dimensions, specifically the anterior facial height, since the increase in growth during puberty is greater compared with other craniofacial structures (Sarnäs and Solow, 1980); and (iii) on the cranial base because of the presence of synchondrosis, which is still active in growth during the pubertal period (Lewis *et al.*, 1985; Ranly, 1988; Figure 2).

Table 1 The medians for statural height (cm) and linear cephalometric variables (mm), at the start of the study and after 1 year for the control group (n = 37) and the delayed puberty boys (n = 7). The significance of the difference between the controls and the delayed-puberty boys is indicated as * (P < 0.05) or ** (P < 0.01).

	Start		After 1 year	
	Control	CDGP	Control	CDGP
Height	160	148*	168	158*
S–N	7.4	7.2	7.5	7.4
S–Ba	4.7	4.6	4.9	4.8
N–Ba	10.9	10.4*	11.2	10.9
N–ANS	5.7	5.4*	5.9	5.6
ANS–Me	6.4	6.1	6.5	6.6
N–Me	11.9	11.7	12.8	12.1
Art–Go	4.5	3.9**	4.7	4.3
Go–Pog	7.8	8.0	7.4	7.8
Art–Pog	10.9	10.4	11.2	10.8

Statistical analysis

Statistical significance was calculated with the Mann–Whitney *U*-test, which is a two-sample (non-matched) unpaired, non-parametric test. A significance level of $P < 0.05$ was used.

Approval

The study was approved by the Institutional Review Board of the Katholieke Universiteit Leuven. Written parental consent was obtained for each participating boy.

Results

The distributions of the different parameter values in the study group and in the control group were compared. Table 1 gives the median, and upper and lower limits of the craniofacial variables. At the start of the study, statural

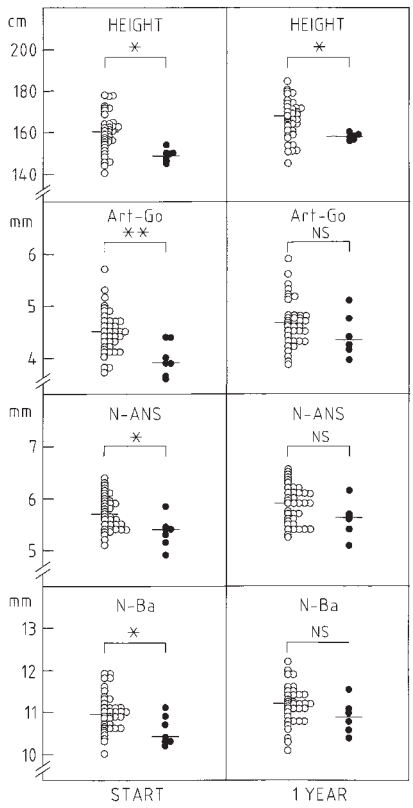

Figure 3 The distribution of statural height, ramus length of the mandible (Art–Go), upper facial height (N–ANS), and total cranial base length (N–Ba) for controls (○; $n = 37$) and delayed-puberty boys (●; $n = 7/n = 6$) at the start of the study and after 1 year. The solid line indicates the median of the group. The significance of the difference between the controls and the delayed puberty boys is indicated as $*P < 0.05$ or $**P < 0.01$.

height, mandibular ramus length (Art–Go), upper anterior face height (N–ANS), and total cranial base length (N–Ba) were significantly smaller in the delayed puberty boys than in the controls (Figure 3). No significant differences were found for mandibular body length (Go–Pog), total length of the mandible (Art–Pog), lower anterior face height (ANS–Me), total anterior face height (N–Me), and for the anterior and posterior cranial base length (N–S; S–Ba).

Comparing the treated CDGP patients with the height-matched control boys in the 1-year period, testosterone treatment was found to have a growth acceleration effect in some craniofacial components similar to that in height. The growth rates of statural height, upper and total anterior face height (N–ANS; N–Me), and ramus/total mandibular length (Art–Go; Art–Pog) were significantly greater in the treated delayed puberty boys than in the height-matched controls (Figure 4). The growth rates of mandibular body length (Go–Pog), lower anterior face height (ANS–Me), and anterior (N–S), posterior (S–Ba), and total (N–Ba) cranial base did not differ significantly between these two groups.

Comparing the distribution of the values of the various parameters after 1 year, the difference in statural height between the treated delayed puberty boys and the controls had diminished, while significant differences could no longer be detected in any of the craniofacial dimensions investigated (Figure 3).

After 1 year, the testicular volume of all the treated delayed puberty boys was larger than 4 ml. However, these testicular volumes were still much smaller than those of normal boys at their full pubertal development (Figure 5).

Discussion

The results in the present study (Figure 3) show that CDGP boys have shorter craniofacial dimensions compared with healthy control boys. The observed growth delay in the mandible, the cranial base and the anterior face height can be explained, as the growth of these structures has been associated with the pubertal growth spurt in height (Hunter, 1966; Mitani, 1973; Baughan *et al*., 1979).

Spiegel *et al*. (1971) noted a similar association between statural height and craniofacial dimensions in children with GH deficiency. In line with our findings, there was an effect on the mandibular ramus length, but no effect on the anterior cranial base length. However, in contrast with delayed puberty, GH deficiency also appeared to have an effect on the lower anterior facial height. Growth retardation of mandibular ramus length, upper anterior facial height and cranial base length has also been demonstrated in short children born small for gestational age (Van Erum *et al.*, 1997).

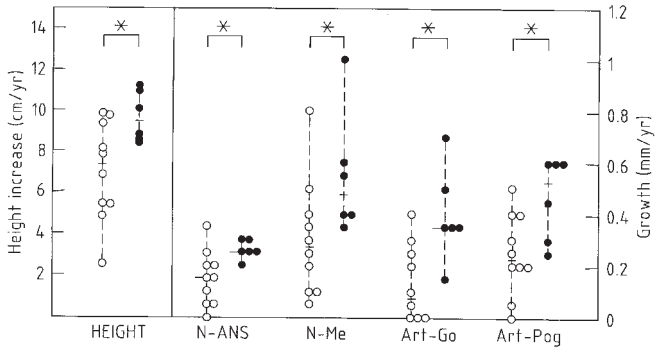

Figure 4 The growth rate of statural height, upper anterior facial height (N–ANS), total anterior facial height (N–Me), ramus length of the mandible (Art–Go), and total length of the mandible (Art–Pog) for the height-matched controls (○; $n = 7$) and the delayed puberty boys (●; $n = 6$) after 1 year. The horizontal bars indicate the median of the group. The significance of the difference between the height-matched controls and the delayed puberty boys is indicated as $*P < 0.05$.

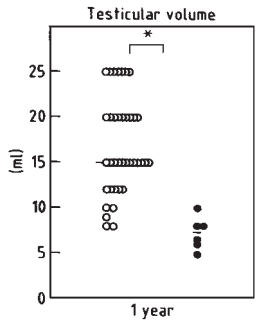

Figure 5 The distribution of testicular volume for the controls (○; $n = 37$) and the delayed-puberty boys (●; $n = 6$) after 1 year. The horizontal bars indicate the median of the groups. The significance of the difference between the controls and the delayed puberty boys is indicated as $*P < 0.05$.

The shorter total cranial base length observed in the delayed puberty boys at the start of treatment is presumably due to the delayed growth of the posterior cranial base, since growth in the anterior part is greatest around the first year of life (Ohtsuki *et al.*, 1982). The posterior part is capable of linear expansion until adolescence, due to the growth of the spheno-occipital synchondrosis (Ranly, 1988).

The purpose of testosterone treatment of CDGP boys is to induce the delayed pubertal growth spurt, and the observed increase in height and testicular volumes after 1 year of treatment indicates the effectiveness of the treatment. The administrated exogenous testosterone may influence growth directly or by influencing (enhancing) the secretion of growth hormone (Kerrigan and Rogol, 1992). The effect of the testosterone treatment on the growth rate of height is thought to result from a combination of these two effects on long bone and vertebral growth (Aynsley-Green *et al.*, 1976; Tanner *et al.*, 1976; Bourguignon, 1988). Evidence for the effect of oestrogens on skeletal growth and development in men through specific androgen receptors has also been reported (Colvard *et al.*, 1989; Smith *et al.*, 1994).

As both GH and testosterone are also known to contribute to mandibular growth (Pirinen *et al.*, 1994), the accelerated growth of the mandible is probably also caused by a combination of the direct and indirect testosterone effects. Evidence that the effect on the ramus is at least partially due to the GH-mediated indirect effect of testosterone is found in a report by Rongen-Westerlaken *et al.* (1993), who found that GH therapy in girls with Turner's syndrome also resulted in an increased mandibular length.

Conclusions

The results show that boys with delayed puberty also have delayed craniofacial development. Low dose testosterone treatment in these subjects not only accelerates the height growth rate, but also those of the craniofacial parameters. At the end of the observation period of 1 year, no significant difference could be observed for any craniofacial parameter between the treated delayed puberty boys and controls, which indicates that testosterone treatment induces a catch-up growth of facial dimensions without signs of disproportional growth.

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