Short stature of prenatal origin: craniofacial growth and dental maturation

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SUMMARY Recently, children born small for gestational age (SGA) with a catch-up growth failure, have been selected for high dose growth hormone (GH) treatment. In order to gain greater insight concerning dentofacial growth and maturation of these patients, and to evaluate the possible effects of high dose GH administration on facial structures, craniofacial growth and dental maturation were evaluated in short SGA persons. Seventy-seven cephalograms and orthopantomograms were available from 48 subjects, aged between 2 and 32 years.

Craniofacial growth was assessed by calculating age- and gender-specific standard deviation scores (SDS) for eight linear and five angular measurements. Tooth formation was evaluated by means of a dental delay score (i.e. dental age minus chronological age).

The SDS for craniofacial growth measurements for the lateral aspect showed a short anterior cranial base (–1.8 SDS), a small retropositioned mandible (≤ –1.7 SDS) and a small maxilla (–1.5 SDS); a high mandibular plane angle (+1.9 SDS) and a wide cranial base angle (+1 SDS). These findings result in a small retrognathic face with a relatively increased lower anterior face height (+1.7 SDS). In contrast to skeletal maturation, dental age was not delayed.

The general growth retardation is, apparently, reflected to a differential extent within the craniofacial complex, while dental maturation appears to be a distinct process tightly linked to chronological age, and independent of general growth and bone age.

Introduction

During the first 2 years of postnatal life, most children born small for gestational age (SGA) (nearly 90 per cent) catch up to a height that is within normal limits for their age (Hokken-Koelega *et al.*, 1995; Karlberg and Albertsson-Wikland, 1995). Some SGA children do not experience a period of sufficient catch-up growth either in infancy or later childhood and remain small. SGA children comprise a very heterogenous group and the aetiology of intra-uterine growth retardation has commonly been differentiated into fetal, placental, maternal, and environmental factors. Chromosomal anomalies and primary growth failure syndromes are examples of intrinsic fetal anomalies interfering with normal fetal growth (Heinrich, 1992). The latter group includes children with Silver–Russell syndrome (SRS). These children demonstrate

typical physical features: low birth weight and/or length for gestational age, characteristic triangular face, relatively prominent forehead, small mandible, clinodactyly of the fifth finger, and a variable body asymmetry (Tanner *et al.*, 1975a; Cullen and Wesley, 1987). These children grow consistently close to or below the 3rd centile without demonstrable endocrine abnormality (Tanner *et al.*, 1975a).

The somatic growth and maturation of the infant into an adult is in many ways reflected by the cephalofacial complex (Bambha, 1961; Brown, 1970; Lewis *et al.*, 1985). Somatic growth in SGA children has been documented (Fitzhardinge and Inwood, 1989; Chaussain *et al.*, 1994; Karlberg and Albertsson-Wikland, 1995), but little is known about the craniofacial development in these individuals. Pioneering studies suggest that facial growth in SGA children is retarded in a way similar to that in children with

hypopituitarism, especially posterior face height measurements were found to be reduced (Spiegel *et al.*, 1971). Cephalometric analysis in SRS children demonstrated small linear dimensions, which were most pronounced in posterior face height and mandibular length (Kotilainen *et al.*, 1995).

The development of the dentition is an integral part of craniofacial growth, even though it is not closely related to other maturational processes. Dental maturation has been shown to be mildly, but consistently delayed in SGA children, although to a lesser degree than skeletal maturation (Garn *et al.*, 1965; Keller *et al.*, 1970) and the degree of reduction in stature exceeds the degree of delay in tooth formation (Ito *et al.*, 1993). Dental maturation was also found to be delayed in many SRS children, but with a high variability (Kotilainen *et al.*, 1995).

In the attempt to normalize the short stature of SGA children, GH administration with low frequency or in low substitution doses, has been explored for many years, but without satisfactory effect. The potential role of GH therapy for SGA children is arousing considerable interest since recent clinical trials have demonstrated that these children increase their height velocity when receiving high dose GH therapy (Stanhope *et al.*, 1991; Chatelain *et al.*, 1994; de Zegher *et al.*, 1996). A possible risk of high dose (two to three times the physiological dose) GH administration is to induce acromegalic effects, but the influence of (high dose) GH therapy on dental maturation is unclear. Thus, it is of interest to gain more insight into the craniofacial growth and tooth formation in untreated SGA children, so that the influence of GH therapy on these various structures can be ascertained.

The aim of this study was to investigate craniofacial growth and dental maturation in SGA males and females between late infancy and early adulthood.

Subjects, materials and methods

Seventy-seven lateral headplates and ortho-pantomograms were obtained from a sample of 48 SGA, non-GH deficient subjects, 25 females and 23 males, between 2.2 and 32.8 years of age.

Thirty-one individuals were part of an ongoing longitudinal study in which the growth promoting effect of high dose GH treatment was investigated. Fourteen of these subjects were untreated and served as controls. From these longitudinal data (on a yearly basis) were used, from the other 17 only the observation at the start of GH treatment was used. All these subjects were followed and/or treated at the Department of Pediatrics at the University Hospital of Leuven, and the data collected between August 1991 and October 1996. At the first visit, mean age ($\pm$ SD) was 8.3 years ($\pm$ 5.8), mean height SDS was –3.1 ($\pm$ 0.9), mean weight SDS was –2.5 ($\pm$ 0.8) and mean bone delay at the first visit was –1.4 years ($\pm$ 1).

The subjects included in this study were selected on the basis of the following criteria: length and/or weight at birth below –2 SD for gestational age and limited spontaneous catch-up growth during postnatal life. Subjects with endocrine disorders, or with major congenital or chromosomal anomalies, and children treated with orthodontic functional appliances were excluded from the study. Sixteen subjects had the physical appearance of Silver–Russell syndrome and two of Dubowitz syndrome.

Somatic growth was assessed by determining height, using a stadiometer, and weight. Height and weight were converted into height SDS and weight SDS, respectively, by using reference curves for height and weight (Karlberg *et al.*, 1976).

To evaluate craniofacial development, standardized lateral cephalograms were traced and 12 landmarks were identified (Figure 1). These landmarks were digitized and 10 linear and six angular measurements were computed by means of the computer program Quick Ceph™ (Orthodontic Processing, Chula Vista, California). Thirty-one cephalograms were measured twice by two independent observers with a one-month interval. No significant ($P > 0.05$) inter- or intra-observer error was found. These measurements were converted into standard deviation scores (SDS) using the Bolton Standards of dentofacial developmental growth (Broadbent *et al.*, 1975). Two linear measurements (S–PNS, S–Go) and one angular (Art–Go–Me) could not be transformed
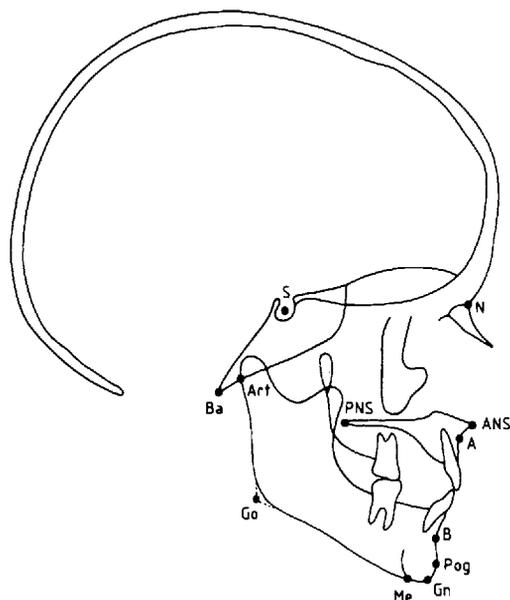
Figure 1 Cephalometric landmarks: A, point A; ANS, anterior nasal spine; Art, articulare; B, point B; Ba, basion; Gn, gnathion, Go, gonion (constructed); Me, menton; N, nasion; PNS, posterior nasal spine; Pog, pogonion; S, sella turcica.

Table 1 Standard deviation scores for height, weight, dental and skeletal age, and ranked SDS separately for linear and angular measurements, with the SD and range for each variable.

	Mean SDS ± SD	Range
Height	−2.8 ± 1	−6.2 to −1.6
Weight	−2.4 ± 0.7	−4.2 to −0.8
Dental age	−0.02 ± 0.7	−1.3 to 1.5
Skeletal age	−1.4 ± 0.9	−3.4 to 1.5
Linear Variables		
Go–Pog	−1.8 ± 1.7	−5.3 to 3.3
S–N	−1.8 ± 1.1	−4.8 to 0.5
Art–Go	−1.7 ± 1.7	−5.9 to 1.5
ANS–PNS	−1.5 ± 1.3	−5 to 0.9
N–ANS	−1.3 ± 1.3	−4.3 to 1.5
S–Ba	−0.8 ± 1.4	−5.3 to 1.6
N–Me	0.1 ± 1.2	−2.2 to 3.5
ANS–Me	1.7 ± 1.3	−2 to 4.8
Angular Variables		
S–N–B	−1.7 ± 2.4	−9.2 to 2.2
S–N–A	−0.9 ± 2	−7.2 to 3.3
N–S–Art	1 ± 1.7	−3.8 to 5.6
A–N–B	1.2 ± 1.5	−3 to 5.3
S–N/Go–Gn	1.9 ± 1.8	−1.9 to 6.5

into SDS due to the lack of equivalent norms in the Bolton series.

All linear measurements were transformed to arrive at the same enlargement as the Bolton data by using the multiplication factor E_B/E_S where E_B is the enlargement factor in Bolton data, and E_S is the enlargement factor in this study.

Dental maturation was assessed from panoramic radiographs using Demirjian's seven-tooth system (Demirjian et al., 1973). For 31 orthopantomograms, this dental age assessment was performed twice by two independent observers with a one-month interval. Neither a systematic nor a significant method error was found. Dental delay, defined as dental age minus chronological age, was used for evaluation. In eight subjects, four adults and four children with a dental age below 3 years, dental age could not be calculated.

Bone ages, used in this study, were all read according to the Tanner–Whitehouse II method (Tanner et al., 1975b). 'Bone delay', defined as bone age minus chronological age, was also used for evaluation.

Results

Although mean height and weight SDS of the study population was below −2, none of the craniofacial variables had a mean SDS below −2 (Table 1).

Figure 2 shows ranked SDS for all cephalometric variables. All linear measurements were decreased, except the lower anterior face height (ANS–Me). A cluster of measurements including mandibular corpus and ramus length (Go–Pog, Art–Go), anterior cranial base length (S–N), upper jaw length (ANS–PNS), and anterior upper face height (N–ANS) show moderate decreases (−1.3 ≥ mean SDS ≥ −1.8). The posterior cranial base length (S–Ba) was shortened the least (SDS = −0.8 ± 0.2) and the lower anterior face height (ANS–Me) was increased
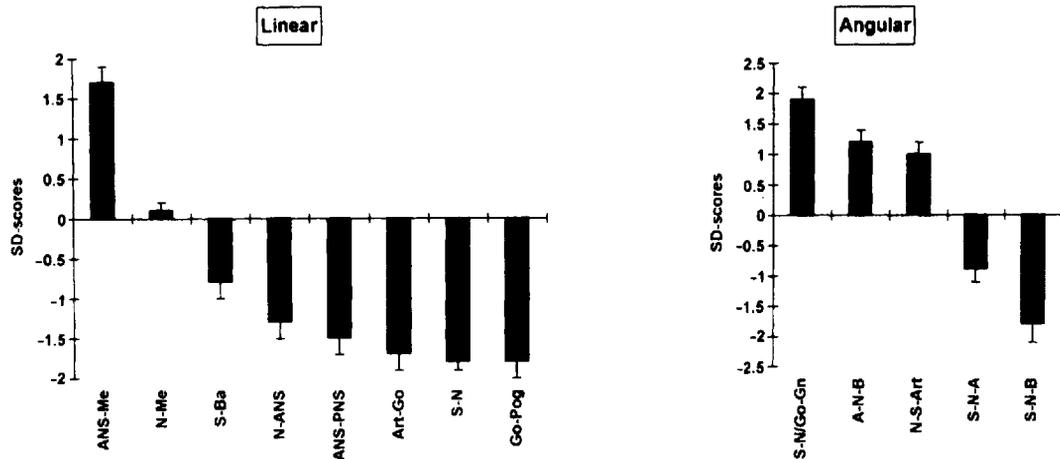
Figure 2   Ranked standard deviation scores (±SEM) separately for linear and angular cephalometric measurements.

(SDS = 1.7 ± 0.2). In combination with a shortened upper anterior face height, the latter result in a normal total anterior face height (N–Me SDS = 0.1 ± 0.1).

Figure 3 shows gender specific scattergrams of all individual linear measurements at the first visit and for all variables, including the upper (S–PNS) and total posterior face height (S–Go) for which SDS could not be calculated. This figure shows the dispersion of all linear measurements for boys and girls.

The SDS for the angular measurements show a high mandibular plane angle (S–N/Go–Gn) (SDS = 1.9 ± 0.2), a wide ANB angle and a wide cranial base angle (N–S–Art); a minimal deficit in the position of the upper jaw in relation to the cranial base (SNA: –0.9 ± 0.2 SDS) and a retro-positioned mandible (SNB: –1.8 ± 0.3 SDS).

Linear regression analyses for the linear and angular craniofacial SDS against chronological age showed no significant association, suggesting that the craniofacial deficits occurred prenatally or during early postnatal growth.

Dental age was found to remain remarkably close to chronological age (Figure 4): mean dental age was –0.02 years ± 0.7 (SD), whereas mean bone delay was –1.4 ± 0.9 (SD). Linear regressions fitted to dental delay scores against bone delay scores showed no significant relationship.

Discussion

In this study the Bolton standards (Broadbent et al., 1975) were used to calculate SDS for craniofacial growth evaluation. This control group appeared most suitable, because matched standards were found for the majority of the observed linear and angular measurements, between the ages of 1 and 18 years. Moreover, the Bolton standards compare well with other standards from mixed-longitudinal origin, e.g. the Denver Growth Study and the Michigan Growth Study (Hunter et al., 1993).

Several linear craniofacial measurements were found to be short in SGA subjects, especially the mandible and the cranial base. Thus, based on Figure 2, it seems that growth retardation is most pronounced in craniofacial components with a high relative and absolute growth potential in childhood (Buschang et al., 1983).

In contrast to most linear measurements, the lower anterior face height is increased. This cephalometric finding may explain the clinical impression that SGA children, especially children with Silver–Russell syndrome, demonstrate a triangular face (Silver et al., 1953; Russell, 1954; Tanner et al., 1975a; Cullen and Welsey, 1987; Kotilainen et al., 1995). An increased lower anterior face height is often found to be
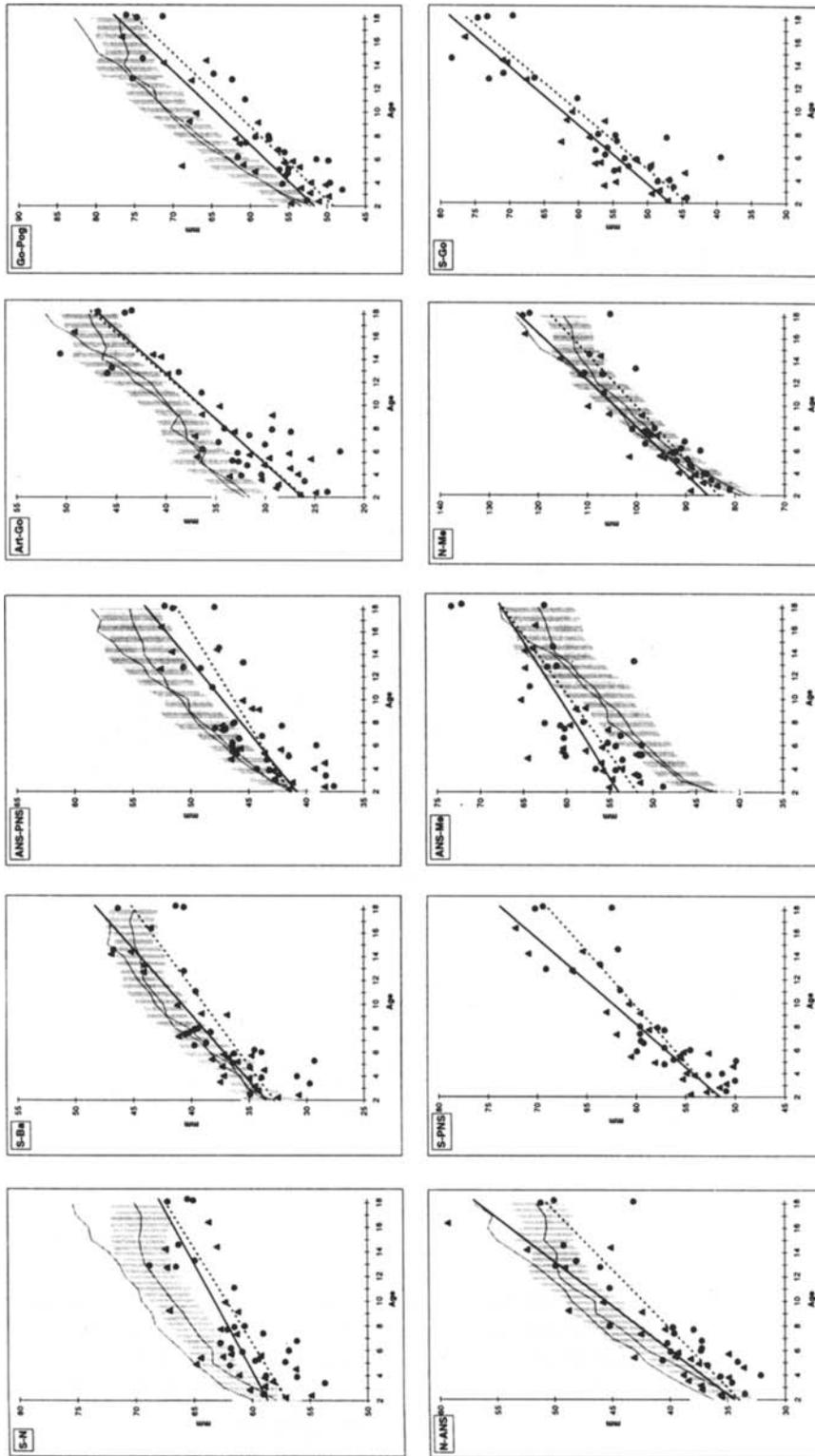
Figure 3 Gender specific scattergrams of individual measurements at the initial visit for all linear cephalometric variables: grey zone = Bolton standards (black line) ± 1 SD (light grey shade for boys, dark grey shade for girls). △ = SGA boys; ○ = SGA girls. Linear trendline: ——— for SGA boys; ·········· for SGA girls.
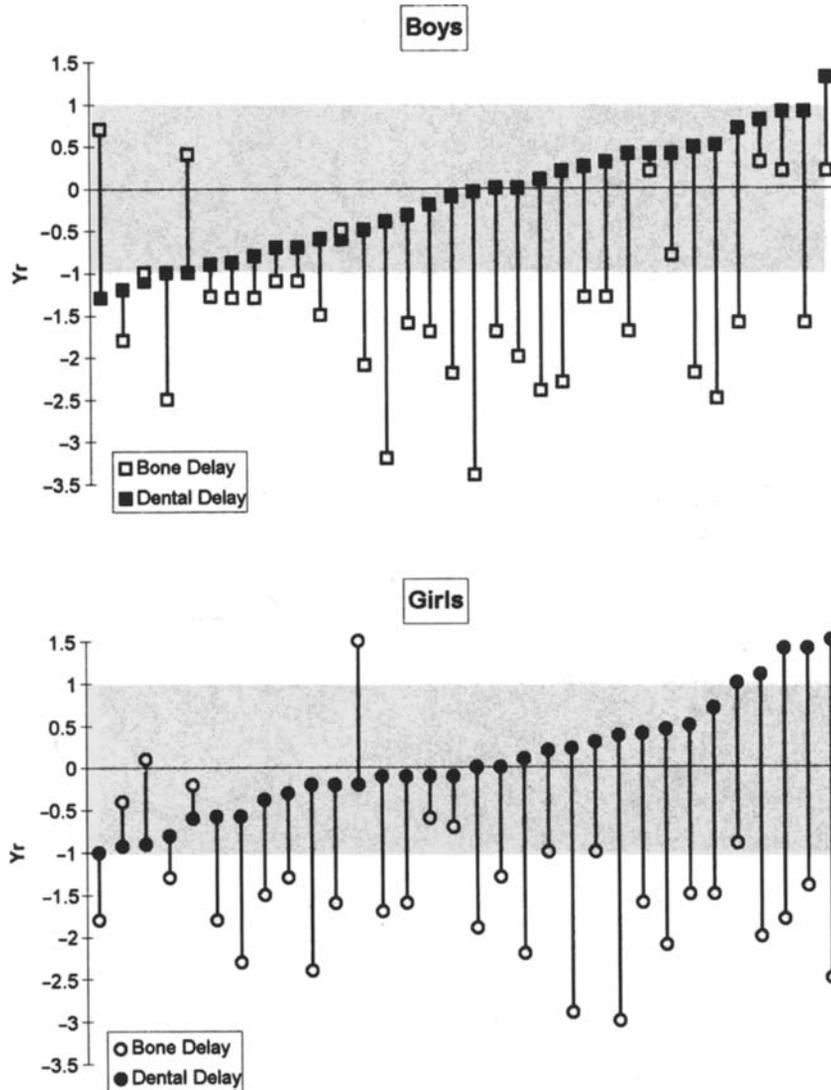
Figure 4 Diagram of ranked dental delay scores (dental age — chronological age) with their corresponding bone delay scores (bone age — chronological age), separately for boys (■) and girls (●).

associated with a wide cranial base and a high mandibular plane angle (Solow and Tallgren, 1976; Bacon *et al.*, 1992). A more obtuse cranial base angle is associated with a more divergent facial type. A lack of growth at the mandibular condyle (e.g. in juvenile rheumatoid arthritis) sometimes gives rise to extreme posterior growth rotations with small posterior and large anterior

face heights (Kreiborg *et al.*, 1990). It is possible that the wide cranial base angle, which has also been demonstrated in SRS patients (Kotilainen *et al.*, 1995), is a sequela of the intra-uterine growth retardation, since it has been shown that the cranial base angle normally decreases during fetal growth (Eynde *et al.*, 1992).The cranial base angle is strongly and negatively correlated with
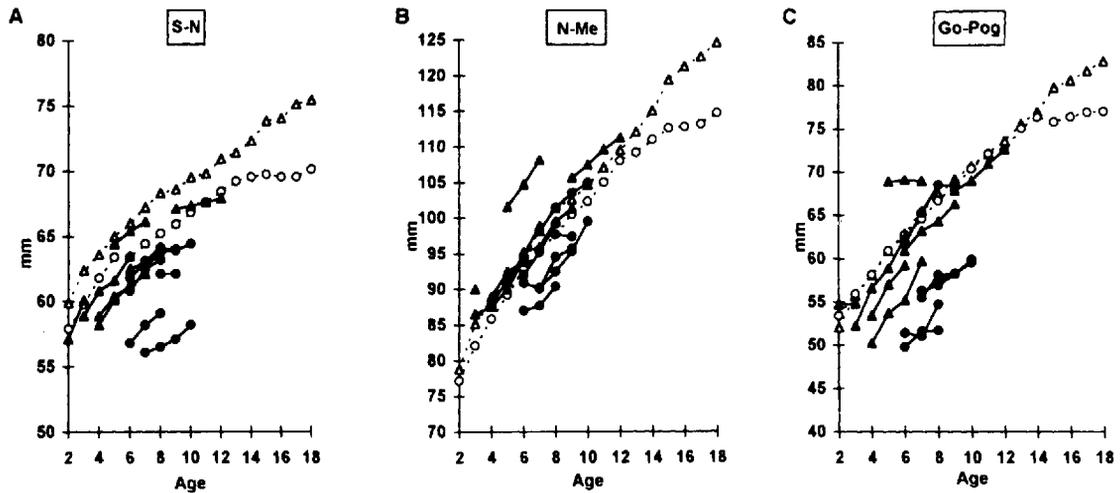
Figure 5 Gender specific diagram of longitudinal data for the linear cephalometric variables: (A) Anterior cranial base length (S–N). (B) Total anterior face height (N–Me). (C) Mandibular corpus length (Go–Pog). Longitudinal data are represented by a black line. ▲ = SGA boys; ● = SGA girls; △ = Bolton standards for boys; ○ = Bolton standards for girls.

the SNB angle as it determines the antero-posterior position of the condyle and the mandible in the facial profile (Kerr and Adams, 1988). The wide cranial base angle and the small mandible explain together the small SNB angle found in SGA children. This theoretical line of thought, as a possible explanation for the cranio-facial growth pattern in these individuals, is maybe rather stretched. The primary differences in this group of SGA subjects are apparently a vertical excess and a mandibular growth defi-ciency, the former possibly caused by the other. Due to the mandibular growth deficiency, the mandible can be rotated backwards and the dento-alveolar compensatory mechanism can be activated vertically in the anterior region to maintain incisal contact for as long as possible.

This study demonstrates that growth retard-ation in SGA children with a catch-up growth failure not only affects their statural height, but also their craniofacial growth, as shown earlier in children with GH deficiency (Spiegel et al., 1971). The literature concerning craniofacial growth in children with pituitary deficiency is rather confined and as the results are not always concordant, it is difficult to compare them with

our cephalometric findings for SGA subjects. GH deficient children show a normal anterior cranial base and upper jaw length (Poole et al., 1982) and a reduced lower anterior face height (Spiegel et al., 1971; Poole et al., 1982), which is in contrast with our findings for SGA children. A striking similarity between SGA and GH deficient chil-dren, is the small mandible, especially the ramus length. Angular measurements were not exten-sively studied in GH deficient children, but Spiegel et al. (1971) found a more flexed cranial base angle. The most pronounced facial growth retardation was found for posterior face height (Spiegel et al., 1971). Although, for posterior face height, a SDS could not be calculated, it can be concluded from the overall facial pattern (divergent facial type) that this measurement is, probably, also small in our group.

In this study, no relationship was found between the age of the subjects and the cranio-facial deficits (SDS), indicating that this condi-tion has a prenatal or early developmental origin. A visual interpretation of the longitudinal data in Figure 5 shows that the SGA children studied have craniofacial growth patterns that evolve in a nearly parallel fashion compared with the

norms, thus indicating a stable condition. This validates the calculated standard deviation scores in this study.

Although our findings suggest that SGA individuals show some typical craniofacial features, it should be noted that there is a high variability in craniofacial growth patterns, as found in a normal population.

Previous studies have reported that tooth formation is retarded in idiopathic short stature (Keller *et al.*, 1970; Ito *et al.*, 1993) and in SRS children (Kotilainen *et al.*, 1995). An increased incidence of GH deficiency or an abnormality in the GH secretory pattern has been observed in SRS children (Stanhope *et al.*, 1989). Since hypopituitarism leads to a delay in dental age (Myllärniemi *et al.*, 1978) this could explain the delay in tooth formation in SRS children. In this sample of SGA individuals (without endocrine disorders), dental age approximated chronological age. Dental age assessment by counting the number of erupted deciduous teeth in children after intra-uterine growth retardation, previously showed that deciduous tooth eruption is also normal (Shuper *et al.*, 1986). These findings support the view that formation and eruption of teeth are processes that are not closely related to general growth.

In contrast to dental maturation, bone maturation was delayed in the majority of the studied cases. In previous studies, low correlations have been reported between dental and skeletal ages in 'normal' subjects (Demirjian *et al.*, 1985; Lewis, 1991).

It can be concluded that SGA subjects show, besides a normal tempo of dental development, a typical facial pattern: small dimensions in the lateral aspect within a divergent face.

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