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Differential growth and maturation in idiopathic growth-hormone-deficient children

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SUMMARY This study describes and compares the growth and maturation of idiopathic growth hormone deficiency (IGHD) and evaluates the potential effects of growth hormone therapy. The sample includes 40 idiopathic growth-hormone-deficient children grouped according to duration of growth hormone replacement therapy. Somatic and craniofacial development, skeletal maturation and dental maturation were evaluated and compared. The results showed consistent delays in the maturity indices for IGHD children. Height age displayed the greatest delay (3 years) followed by skeletal age (2.2 years) and dental age (0.8 years). Overall craniofacial growth deficiencies were also demonstrated. Anterior cranial base and mandibular length were most affected; posterior cranial base length and facial heights were least affected. Analysis of covariance, controlling for the starting age of therapy, showed significant differences between children grouped according to duration of growth hormone therapy. Catch-up growth with hormonal therapy was established for height, facial height, skeletal age and posterior cranial base length. It was concluded that the various craniofacial skeletal components have different potentials for growth retardation with IGHD; catch-up growth following growth hormone replacement therapy was greatest for the components with the greatest initial (or baseline) growth potential.

Introduction

Control of postnatal craniofacial skeletal growth involves complex interactions of genes, hormones and nutrients. Local control of growth and remodelling is influenced by tissues in close proximity to the skeletal structures; general control pertains to systemic factors that can influence distant structures such as hormones (Van Limborgh, 1970).

Linear somatic growth and maturation are influenced and controlled by various hormones, particularly pituitary growth hormone (Wilson and Foster, 1992; Rubenstein and Federman, 1989). Since the influence of growth hormone therapy on growth depends on its duration, timing and extent (Hernandez *et al.*, 1977; Milner *et al.*, 1979; Perlman and McLellan, 1991), its effects on different target tissues might be expected to vary on the basis of their different growth potentials. In acromegaly, for example, excess growth hormone production after puberty results in large mandibles and coarse facial features (Rubenstein and Federman, 1989; DiGeorge, 1992; Wilson and Foster, 1992), structures which have the greatest potential for growth. While an association between craniofacial and somatic development has been clearly established (Nanda, 1955; Hunter, 1966; Woodside, 1974; Mitani, 1977; Moore *et al.*, 1977; Baughan *et al.*, 1979; Ekström, 1982; Fishman, 1982; Buschang *et al.*, 1983; Proffit, 1986), the effect of growth hormone on the individual craniofacial bony components should be, nevertheless, quite variable. Given the various tissues involved in craniofacial development, a wide range of relationship might be expected between a child's general somatic growth pattern and the growth of his/her craniofacial components. As such, the potential of an individual component to respond to hormonal differences or therapy should be related to the relative craniofacial maturity gradient (Buschang *et al.*, 1983), which ranges from skeletal structures influenced primarily by the growth of neural tissues (cranium) to structures under more direct

somatic control (mandible). In contrast, dental development has been shown to have little or no relationship with skeletal or somatic maturation (Demirjian *et al.*, 1985).

Individuals with growth hormone deficiency display significant maturational delays and reduced somatic growth. Growth failure can usually be established by the age of 2–4 years of age (Wilson and Foster, 1992), at which time skeletal age may be delayed by up to 2 years (Garn *et al.*, 1965; Guyda *et al.*, 1975; Kosowicz and Reymski, 1977; Takano *et al.*, 1986; Sarnat, 1988; Rubenstein and Federman, 1989; Perlman and McLellan, 1991). Studies have also shown that height is somewhat more affected by growth hormone deficiency than skeletal maturation, even though both follow similar developmental patterns (Guyda *et al.*, 1975; Lanes *et al.*, 1979; Milner *et al.*, 1979). As indicated, however, dental development of children with growth hormone deficiency is characteristically less affected than either somatic growth or skeletal maturation (Poole *et al.*, 1982; Sarnat, 1988).

The literature pertaining to craniofacial development suggests that growth hormone deficiency results in an immature facial appearance (Kosowicz and Reymski, 1977; Sarnat, 1988). The length and depth of the face are inappropriately small for the age, with the face maintaining a child-like convexity (Bevis *et al.*, 1977). In females, the anterior cranial base appears normal, while the posterior cranial base length is short; males, in contrast, show an overall general reduction in cranial base size (Spiegel *et al.*, 1971; Konfino *et al.*, 1975). Most studies have reported relatively smaller posterior cranial bases versus anterior (Markus *et al.*, 1942; Konfino *et al.*, 1975; Poole *et al.*, 1982), and that the maxilla is similarly reduced in size (Poole *et al.*, 1982; Takano *et al.*, 1986). In fact, the maxillae in Konfino *et al.*'s (1975) sample of severely deficient patients (Laron type of growth hormone deficiency) averaged –3.9 SD below the mean. Total mandibular length is reduced, primarily as a result of a smaller ramal height (Markus *et al.*, 1942; Takano *et al.*, 1986; Sarnat, 1988). Finally, face heights have been found to be smaller posteriorly than anteriorly, producing the steep mandibular plane angle seen frequently in patients with growth hormone deficiency (Markus *et al.*, 1942; Garn *et al.*, 1965; Kosowicz and Reymski, 1977; Poole *et al.*, 1982; Takano *et al.*, 1986).

Treatment of growth hormone deficiency produces a 'catch-up' phenomenon in both height and skeletal maturation, especially during the first year of replacement therapy (Guyda *et al.*, 1975; Milner *et al.*, 1979; Romshe and Sotos, 1980; Burns *et al.*, 1981; Cara and Johanson, 1990; Perlman and McLellan, 1991). Although their response to therapy is not as pronounced, short normal children also show a positive response to growth hormone regardless of their diagnostic differences (Hindmarsh and Brook, 1987; Moore *et al.*, 1993; McCaughey *et al.*, 1994). It remains controversial, however, whether dental development in growth-hormone-deficient children is affected by treatment (Garn *et al.*, 1965; Bevis *et al.*, 1977; Myllärniemi *et al.*, 1978; Kosowicz and Reymski, 1977; Poole *et al.*, 1982; Takano *et al.*, 1986; Sarnat, 1988). Studies of craniofacial measurements in treated idiopathic growth-hormone-deficient (IGHD) children are limited due to small sample size and conflicting results. The available evidence suggests that facial convexity decreases, mandibular length increases, lower face height increases, arch width remains constant and cranial base length shows minimal change (Bevis *et al.*, 1977; Poole *et al.*, 1982). Poole *et al.* (1982) also noted that maxillary length was of normal size before GH treatment and that it increased disproportionately with treatment.

In view of the lack of information available for craniofacial development, especially as to its association with indices of skeletal, dental and somatic development, this project aimed to evaluate the differential growth and maturation of craniofacial structures in IGHD children during treatment with replacement therapy. The only other study (Poole *et al.*, 1982) to evaluate simultaneously the various aforementioned indices, was based on a results-limiting sample of 10 subjects.

Subjects and methods

Data was obtained from a cross-sectional sample

of 40 patients (21 males and 19 females) selected using the following criteria:

1. A diagnosis of isolated IGHD based on longitudinal height data below the third percentile, a subnormal growth relevant for age and a growth hormone level below 10 ng/ml after stimulation with at least two of the following: L-DOPA, arginine and/or clonidine.
2. No known history of brain tumours and/or prior central nervous system radiation therapy.
3. Age 5–18 years.
4. Growth hormone, when given, must have been administered in doses of 0.3 mg/kg/week s.c. 3–6 times per week.

The sample was divided into three groups based on the duration of growth hormone replacement therapy. A group of 14 untreated (less than 0.2 years of therapy) children was compared with 13 subjects who had received short-term therapy (0.2–2.0 years) and 13 subjects with long-term therapy (2.0+ years). The groupings were based on available records, which could produce selection bias. The mean age of the untreated group was 10.7 years; the mean ages of the short- and long-term groups at the start of treatment were 8.6 and 7.1 years, respectively. Potential age and gender effects were addressed by converting each subject's measurements to *Z*-scores using age- and gender-specific reference data.

Standing height was measured using a stadiometer and standard methodology (Hindmarsh and Brook, 1986). Three measurements, which differed by no more than 0.3 cm, were recorded and averaged. Replicate analysis of 15 individuals showed no significant systematic error and a method error of 0.22 cm. Each subject's height was converted to *Z*-scores based on US reference data (Hamill, 1977).

Skeletal maturation was assessed from hand–wrist radiographs using the FELS method (Roche *et al.*, 1988). Replicate analyses showed no systematic error and a method error of 0.25 years. Each subject's skeletal age was converted to *Z*-scores based on US reference data (Roche *et al.*, 1988).

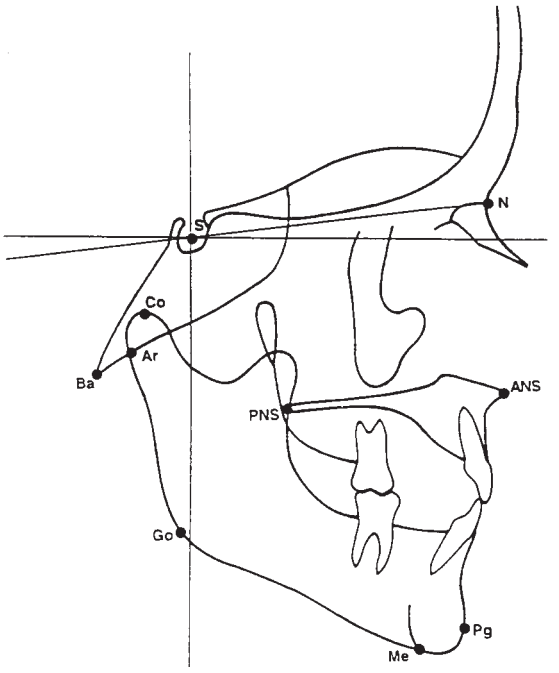

Figure 1 Cephalometric landmarks.

Dental maturation was assessed from panoramic radiographs using Demirjian's seven-tooth system (Demirjian, 1986). Replicate analyses showed no systematic error and a method error of 0.30 years. *Z*-scores were not calculated since the reference data were not normally distributed (Demirjian, 1986). Dental delay, defined as dental age minus chronological age, was used for the evaluations.

To evaluate craniofacial development, standardized lateral cephalograms were traced and 10 landmarks (Riolo *et al.*, 1974) were identified (Figure 1). The landmarks were digitized and eight measurements were computed (Table 1). Replicate analyses showed no systematic errors; random method errors ranged between 0.38 and 0.77 mm. The measures were converted to *Z*-scores using established reference data (Riolo *et al.,* 1974).

Results

In comparison with their mean chronological age, the subjects showed a consistent matura-

Table 1 Systematic and random technical errors of the cephalometric measurements

Abbreviation	Measure	Systematic error		Random method error (mm)
		Mean (mm)	SE	
S–N	Sella–Nasion (anterior cranial base length)	0.04	0.14	0.38
S–Ba	Sella–Basion (posterior cranial base length)	0.06	0.20	0.54
PNS-ANS	Posterior–Anterior Nasal Spine (maxillary length)	0.00	0.19	0.50
Co–Pg	Condylion–Pogonion (total mandibular length)	0.19	0.25	0.68
Co–Go	Condylion–Gonion (ramus height)	–0.01	0.29	0.77
Go–Pg	Gonion–Pogonion (corpus length)	–0.31	0.24	0.66
N–Me	Nasion–Menton (anterior facial height)	0.09	0.17	0.45
S–Go	Sella–Gonion (posterior facial height)	0.30	0.17	0.49

Table 2 Chronological and physiological ages (years) at baseline.

Ages	Mean	SD	Min	Max
Chronological	10.4	2.4	6.0	15.9
Dental	9.6	2.4	4.4	14.9
Skeletal	8.2	2.7	3.2	13.8
Height	7.4	2.1	3.9	11.7

Table 3 Ranked *Z*-scores for height, skeletal age and the craniofacial size measurement

Measurement	Mean	SD	Min	Max
S–N	–2.6	1.1	–4.6	–0.5
Height	–2.5	1.4	–5.9	0.5
Co–Pg	–2.2	1.7	–6.0	2.2
Go–Pg	–2.0	1.7	–5.4	3.3
Skeletal age	–1.8	1.7	–5.4	1.3
N–Me	–1.7	1.2	–4.9	2.1
S–Go	–1.6	1.5	–4.8	2.8
PNS–ANS	–1.5	1.0	–3.6	1.2
S–Ba	–1.2	1.1	–3.9	0.6
Co–Go	–1.1	1.6	–4.3	3.9

tional delay (Table 2). Height age was delayed by approximately 3 years, followed by skeletal age (2.2 years) and dental age (0.8 years).

Z-scores for height, skeletal age and craniofacial size showed considerable variability across all measurements (Table 3). The *Z*-scores for measures of anterior cranial base (S–N) were the smallest, followed closely by height. A cluster of measures including mandibular length (Co–Pg), corpus length (Go–Pg), skeletal age, anterior facial height (N–Me), posterior facial height (S–Go), and maxillary length (ANS–PNS) showed only moderate ($-1.5 \geq Z\text{-score} \geq -2.2$) deficits. Posterior cranial base length (S–Ba) and ramus height (Co–Go) were the least delayed ($-1.1 \geq Z\text{-score} \geq -1.2$).

Analyses of covariance, controlling for age at start of therapy, showed significant effects of treatment duration for five of the 11 measurements (Table 4). Height, skeletal age, anterior facial height (N–Me), posterior facial height (S–Go) and posterior cranial base length (S–Ba)

Table 4 Analysis of covariance evaluating duration of growth hormone replacement therapy with start of treatment as the covariate.

Z-scores	Source	MS	*F*	*P*
SN	Start (S)	0.06	0.05	NS
	Duration (D)	1.02	0.87	NS
	Residual (R)	1.17		
Height	S	12.64	7.52	**
	D	15.81	9.41	***
	R	1.68		
Co–Pg	S	20.45	8.17	**
	D	4.28	1.71	NS
	R	2.50		
Go–Pg	S	11.23	4.33	*
	D	2.22	0.86	NS
	R	2.59		
Skeletal age	S	25.18	27.11	***
	D	8.16	8.78	***
	R	0.93		
N–Me	S	2.09	1.58	NS
	D	4.51	3.40	*
	R	1.33		
S–Go	S	7.69	4.13	*
	D	7.71	4.14	*
	R	1.86		
PNS–ANS	S	0.01	0.01	NS
	D	1.75	1.62	NS
	R	1.08		
S–Ba	S	1.00	1.00	NS
	D	4.26	4.17	*
	R	1.02		
Co–Go	S	13.40	5.96	*
	D	5.02	2.23	NS
	R	2.25		
Dental delay (years)	S	12.92	8.38	**
	D	2.95	1.92	NS
	R	1.54		

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

demonstrated significant differences between the untreated, short- and long-term groups. Age at the start of growth hormone replacement therapy had a significant effect for seven of the 11 measurements. There was no effect of starting age on anterior (S–N) and posterior cranial base lengths (S–B), anterior facial height (N–Me) or maxillary length (ANS–PNS). Table 5 shows the greatest effect of replacement therapy in height and skeletal age, which showed improvements ranging between 2.2 and 2.8 standard units. Posterior facial height (S–Go) showed a greater improvement than either anterior facial height (N–Me) or posterior cranial base length (S–Ba).

Table 5 Estimated duration effects adjusted for start of growth hormone treatment.

Measure	Grand mean (*Z*-scores)	Duration group[1]	Deviations from grand mean
Height	–2.51	Untreated (U)	–1.00
		Short-term (S)	–0.03
		Long-term (L)	1.22
Skeletal age	–2.50	U	–1.49
		S	0.52
		L	1.30
N–Me	–1.74	U	–0.73
		S	0.26
		L	0.52
S–Go	–1.62	U	–0.76
		S	–0.14
		L	0.95
S–Ba	–1.18	U	–0.57
		S	–0.09
		L	0.70

Discussion

In terms of the sample patients' height and skeletal maturation, the observed deficits due to growth hormone deficiency as well as their associated catch-up with replacement therapy followed expected patterns. The untreated group was delayed in height by approximately 3.8 standard units, which is consistent with the –2.0 to –4.8 range previously reported (Gudya *et al.,* 1975; Milner *et al.*, 1979). The treated children clearly showed significant catch-up in growth and maturation, also as previously described (Garn *et al.,* 1965; Gudya *et al.,* 1975; Sarnat, 1988; Perlman and McLellan, 1991). While Guyda and co-workers (1975) showed that height age approached chronological age after therapy, our long-term group remained approximately 1 SD below the mean after more than 2 years of replacement therapy. In this respect, prior studies have repeatedly shown that catch-up with replacement therapy for height and skeletal age was greatest during the first 2 years of treatment (Milner *et al.*, 1979; Cara and Johanson, 1990; Perlman and McLellan, 1991).

The mean delay in dental age of our sample was less than 1 year. As previously reported (Poole *et al.*, 1982; Sarnat, 1988), dental delay

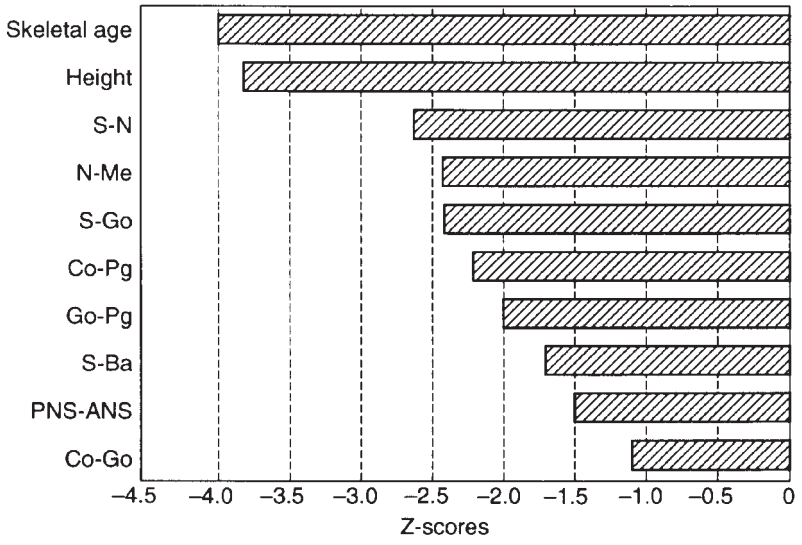

Figure 2 *Z*-scores for somatic and craniofacial measurement of untreated IGHD children.

was significantly less than the delay in skeletal age. Further, there was no significant growth hormone treatment effect on dental maturation, as shown in prior studies (Kosowicz and Reymski, 1977; Poole *et al.*, 1982). The smaller delay and the lack of a subsequent therapeutic response would indicate that dental age is less influenced by and less sensitive to growth hormone than somatic and craniofacial growth. The consistency of results across studies demonstrate that the dental age findings, along with those relating to skeletal age and standing height, of this limited sample of children are representative of the affected population as a whole.

Our results additionally show that growth hormone clearly has less of a positive effect on craniofacial bony development than on somatic (height) growth or overall skeletal maturation. These findings suggest that height and skeletal age have a greater potential for insults as a result of cumulative negative effects, thus substantiating their role as accurate measurements of overall body size and maturational development.

As shown in Figure 2, comparing various baseline parameters in our untreated growth-hormone-deficient children, the effects of growth hormone deficiency grade downward from

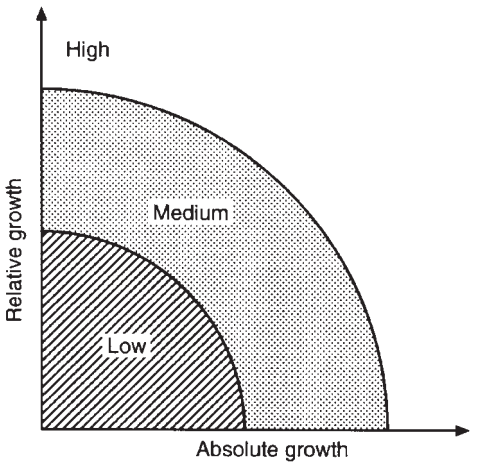

Figure 3 Relationship between relative and absolute growth determines potential (high, medium or low) for growth deficits with IGHD and catch-up with replacement therapy.

skeletal age to ramus height (Co–Go). This gradient implies a relationship between the measure's absolute and relative growth potential, with absolute and relative potentials defined by the actual amount and timing of growth respectively (Figure 3). In this context, Ohtsuki *et al.* (1982) have shown that the anterior cranial base displays its highest rates of growth during

the first two years of life. Moreover, the sphenoethmoidal synchondrosis fuses during childhood, suggesting that the external cranial base had very limited relative growth potential at the time of the initial evaluation of untreated growth-hormone-deficient patients. As a result, the baseline anterior cranial base measurement was greatly affected due to its low residual relative and absolute growth potential. In contrast, ramus height (Co–Pg) was less affected since it retains a greater amount of relative and absolute growth potential through childhood (Buschang *et al.,* 1983).

The patients' craniofacial measurements also showed differential responses to growth hormone replacement therapy. As shown previously, GH treatment produced significant effects in our patients for posterior cranial base length and facial height. Poole *et al.* (1982) reported increased rates of growth for anterior lower facial height and cranial base measurements in five of their eight treated cases. Spiegel and co-workers (1971) reported similar increases. These results support the notion that growth hormone stimulates cartilaginous growth at the spheno-occipital synchondrosis (Petrovic *et al.,* 1990). More importantly, our results again imply that facial dimensions with the greatest growth potential (Figure 3) display the greatest catch-up responses in IGHD patients treated with replacement. Given that it is well established that vertical facial growth has the greatest potential for postnatal growth (Singh and Savara, 1966; Savara and Singh, 1968; Buschang *et al.*, 1983), it is not surprising that craniofacial measurements addressing this dimension showed a significant catch-up phenomenon during the IGHD treatment intervention.

Interestingly, however, ramus height (Co–Go), which has a maturity pattern that closely follows the height pattern (Buschang *et al.*, 1983) failed to display any significant catch-up. There are two possible explanations for this: (i) the development of ramus height is not, in fact, closely related to either posterior cranial base or facial height, and therefore would not be expected to respond; (ii) since ramus height was the least affected of the individual measurements, catch-up may depend not just on growth potential, but also on the extent of accumulated growth defects at the start of growth hormone replacement therapy.

In our study, antero-posterior growth of the maxilla was not affected by growth hormone therapy, as previously suggested (Bevis *et al.*, 1977; Poole *et al.,* 1982). While stimulation of the cartilaginous nasal septum might be expected to increase maxillary length in younger children (Scott, 1953; Baume, 1961), the treated IGHD patient groups, who were on average 7.1 and 8.6 years of age respectively at the start of treatment, might have been too old at the baseline to have benefited significantly from any potential growth effect from corrective therapy. In fact, prior studies have already shown that anterior–posterior growth of the nasal septum decreases substantially around the age of 7 years (Scott, 1953, 1959). Similarly, anterior–posterior growth of the mandible was likewise unaffected by growth hormone replacement therapy—a lack of response which might be attributed more to its relationship with the maxilla (Enlow, 1990; Petrovic *et al.,* 1990) than merely to its more limited growth potential.

Conclusions

In summary, it is concluded that somatic growth, skeletal maturation, dental calcification and craniofacial development are all deficient in IGHD children prior to the initiation of replacement therapy. Furthermore, the extent of these deficiencies varies across individual measurements, supporting the different potentials for growth retardation inherent in each of these target tissues. These results suggest significant implications as to the timing of replacement therapy; they certainly imply that therapy should commence as early as possible before the development of detrimental discrepancies. Finally, catch-up growth following GH therapy appears to be most pronounced for tissues under intrinsic control. Other craniofacial structures under alternate control show varying responses to therapy, some of which may potentially result in undesirable, non-physiological craniofacial growth patterns.

Longitudinal studies are undoubtedly necessary, not only to corroborate and extend our findings, but also to confirm the absence of an iatrogenic maldevelopmental effect with more prolonged growth hormone administration on craniofacial structures with a limited baseline growth potential.

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