Original Article

Effects of Growth Hormone on Craniofacial Growth

Duration of Replacement Therapy

Minayo Funatsu[a]; Koshi Sato[b]; Hideo Mitani[c]

ABSTRACT

Objective: This study determined the effects of growth hormone (GH) therapy on craniofacial growth in idiopathic growth hormone deficiency (GHD).

Materials and Methods: Fifty-seven patients (33 boys and 24 girls; age range 4.5 to 16.7 years) with GHD were investigated and categorized into three groups according to the duration of GH therapy: the untreated group, the short-term therapy group, and the long-term therapy group. Their lateral cephalometric radiographs were studied, and craniofacial measurements were assessed by age and sex by using matched standard deviation scores.

Results: In the untreated group, the anterior cranial base, total facial height, maxillary length, mandibular total length, mandibular body length, and ramus height were smaller than the standard values. In comparison with the untreated group, the long-term therapy group had a significantly larger upper facial height ($P < .05$), maxillary length ($P < .01$), and ramus height ($P < .01$) measurements.

Conclusions: Children who received long-term GH replacement therapy showed increased growth of the craniofacial skeleton, especially the maxilla and ramus. These findings suggest that GH accelerates craniofacial development, which improves occlusion and the facial profile.

KEY WORDS: Growth hormone deficiency; Growth hormone replacement therapy; Craniofacial skeleton; Maxillary length; Ramus height; Upper facial height

INTRODUCTION

Many factors affect growth between birth and adulthood, including chromosomal aberrations such as Turner syndrome; endocrine abnormalities caused by growth hormone deficiency (GHD); bone and cartilage abnormalities such as chondrodysplasia; chronic disorders of the main organs such as renal failure; insufficient or defective absorption in the colon; and metabolic disorders such as diabetes, chronic strumitis, maternal deprivation syndrome, and anorexia nervosa.[1] Furthermore, hormone secretion plays an important role in homeostasis in vivo. Hormones affecting growth include pituitary, thyroid, adrenocortical, and sex hormones, as well as insulin.

Growth hormone (GH), which is secreted by the pituitary, plays an important role in longitudinal bone growth.[2] GHD is a disease that leads to growth disturbances, mainly short stature, as a result of inhibited pituitary gland hormones. Its causes can be classified as idiopathic, organic, or genetic. Idiopathic abnormalities of cryptogenic cause are the most common (more than 80%); the specific therapy for idiopathic GHD (IGHD) is GH replacement therapy.[3]

With IGHD, the length and depth of the face are inappropriately small for the child's age, with the face maintaining childlike convexity.[4] Many studies have reported mandibular total length (Gn-Cd) is reduced, primarily as a result of the small ramus height (Cd-Go).[5–9] In addition, the maxilla is significantly reduced,[5] and there may be a comparable degree of reduction in the mandible.[6,7] The maxilla is often retrognathic but is affected less than the mandible.[8,9] Concerning cra-

[a] Postdoctoral, Division of Orthodontics and Dentofacial Orthopedics, Department of Oral Health and Development Sciences, Graduate School of Dentistry Tohoku University, Sendai, Japan.

[b] Assistant Professor, Division of Orthodontics and Dentofacial Orthopedics, Department of Oral Health and Development Sciences, Graduate School of Dentistry Tohoku University, Sendai, Japan.

[c] Professor Emeritus, Tohoku University, Sendai, Japan.

Corresponding author: Minayo Funatsu, DDS, PhD, Division of Orthodontics and Dentofacial Orthopedics, Department of Oral Health and Development Sciences, Graduate School of Dentistry, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan (e-mail: hunatsu@mail.tains.tohoku.ac.jp).

Accepted: November 2005. Submitted: January 2005.

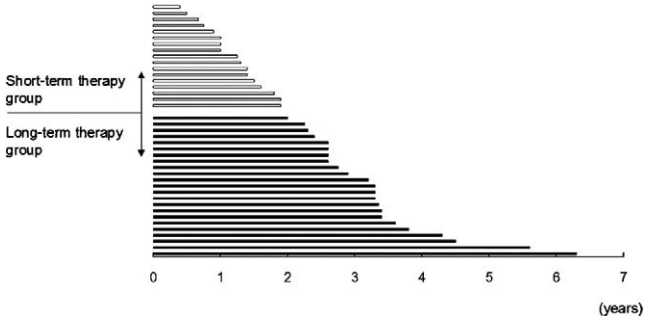

Figure 1. Duration of growth hormone therapy.

nial base size, many studies have reported that the posterior cranial base length is smaller than the anterior cranial base (N-S) length.[5,7,9] By contrast, facial convexity decreases with GH replacement therapy, and its main effect seems to be on condylar growth.[4] Another study reported that growth in the Gn-Cd and lower facial height (ANS-Me) are accelerated, whereas the cranial base length changes minimally.[7] Cantu et al[9] found that catch-up growth with GH therapy affects the anterior facial height, posterior facial height, and posterior cranial base.

Many of these studies were based on a small number of subjects, and the results were variable. Moreover, the effect of GH therapy on final body height is affected by the length of administration, dose, frequency, and age at which therapy was started.[10] There are no reports on the effect of the length of administration on craniofacial growth. Therefore, the present study determined the effect of GH therapy on craniofacial growth in IGHD by comparing short- and long-term administration of GH.

MATERIALS AND METHODS

The subjects consisted of 57 patients (33 boys and 24 girls) who came to a special hospital for endocrine diseases and were diagnosed with IGHD according to the following criteria: (1) age-matched height standard deviation (SD) score was below −2 or growth rate per year was below −1.5 SD over 2 years, (2) poor GH responses (peak GH value to provocation test was below 10 μg/L) to two provocative stimuli or the poor GH response to at least one stimulus and significantly low insulin-like growth factor I (IGF-I) value, or (3) low mean nocturnal GH value (below 3 μg/L) for 3-hour samplings at 20-minute intervals together with low IGF-I and low urinary GH values despite normal GH responses to exogenous stimuli. After registration with the Foundation for Growth Science, these patients were treated with recombinant human GH with the dose of 0.5 IU = 0.17 mg/kg per week mainly 6 to 7 times a week. The subjects did not include patients with severe malocclusions or skeletal deviation or patients with other syndromes.

The subjects were categorized into three groups: the untreated group (9 boys and 8 girls; average age 10.9 years), the short-term therapy group (treatment for 0.4 to 2.0 years; 10 boys and 7 girls; average age 11.4 years; average duration of GH replacement 1.2 years), and the long-term therapy group (treatment for more than 2.0 years; 14 boys and 9 girls; average age 12.4 years; average duration of GH replacement 3.3 years) (Figure 1; Table 1).

Because catch-up growth after GH replacement therapy is greatest during the first 2 years,[11,12] we set the cut-off between the short- and long-term therapy groups as 2 years of GH therapy.

Two cephalometric radiographs (one in centric occlusion and the other wide open) and hand-wrist radiographs were exposed. Wide-opening lateral cephalometric radiographs were performed to identify the mandibular condyle. The images in cephalometric radiographs are 1.0625 times the actual size. The hand-wrist radiographs of one boy and one girl and the body height measurements of three girls were not performed.

Body height and radiographs were obtained on the same day at the Department of Orthodontics, Tohoku University Dental Hospital, Sendai, Japan. The bone age was calculated by Japanese standards with the Tanner-Whitehouse 2 method.[13] The mean bone age was 9.5 years for the untreated group, 10.2 years for the short-term therapy group, and 11.6 years for the long-term therapy group. The mean SD score of body height was −2.2 for the untreated group, −2.0 for the short-term therapy group, and −1.7 for the long-term

Table 1. Cross-sectional Sample of 57 Patients (33 Boys and 24 Girls With Diagnosed Growth Hormone Deficiency) (Mean ± SD)

	Untreated Group	Short-term Therapy Group	Long-term Therapy Group
Subjects			
Chronological age, y	10.9 ± 3.05	11.4 ± 2.77	12.4 ± 2.93
Bone age, y	9.5 ± 3.33	10.2 ± 2.54	11.6 ± 2.85
Body height (SD score)	−2.2 ± 0.72	−2.0 ± 0.90	−1.7 ± 0.99
Duration of growth hormone replacement therapy, y	—	1.2 ± 0.47	3.3 ± 1.05
Starting age of growth hormone replacement therapy, y	—	10.2 ± 2.89	9.1 ± 3.04

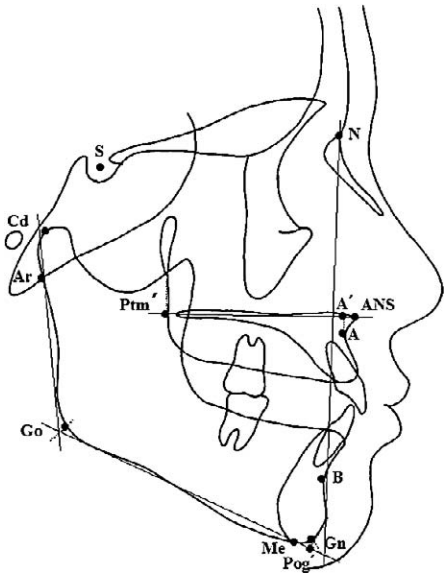

Figure 2. Landmarks and reference lines used for the linear and angular measurements of the lateral cephalogram.

therapy group. This study used the body height standard reported by Suwa et al.[14] After tracing standardized lateral cephalograms, we identified 12 landmarks[15] (Figure 2).

We obtained standard SD scores for Japanese subjects[15] of the same sex and similar age. The SD score was calculated as measurements minus standard value divided by 1 SD. Japanese cephalometric standard values[15] were based on ideal occlusion. The magnification of the x-rays adjusted to its of the reference group.

Statistical Analysis

The *t*-test was used to compare the standard values with the measurements for each IGHD group. After we conducted a one-way analysis of variance in the untreated, short-term therapy, and long-term therapy groups, we compared the differences by Fisher PLSD, which is a multiple comparison test.

RESULTS

Characteristics of the Craniofacial Morphology

Untreated group. We compared the mean values for individuals with IGHD and the standard values for individuals of the same sex and similar chronological age group. Among boys, ANS-Me, maxillary length (A′-Ptm′), Gn-Cd, mandibular body length (Pog′-Go), and Cd-Go were significantly smaller than the standard values. Among girls, ANS-Me, Gn-Cd, and Pog′-Go were significantly smaller than the standard values. The SNA, SNB, and gonial angles were smaller than the standard values (Table 2).

Short-term therapy group. Among boys, the Cd-Go was significantly larger, whereas the SNA and gonial angles were significantly smaller. Among the girls, the gonial angle was significantly smaller than the standard values (Table 3).

Long-term therapy group. Among boys, total facial height (N-Me), ANS-Me, A′-Ptm′, Pog′-Go, and Cd-Go were significantly smaller than the standard values. The mandibular plane was flat, and the gonial angle was significantly smaller. Among the girls, ANS-Me, Cd-Go, and gonial angle were significantly smaller,

Table 2. Linear and Angular Measurements of the Untreated Group—Mean ± SD of the Cephalometric Measurements of the Growth Hormone Deficiency and the Reference Groups[a,15]

	Boys			Girls		
	Untreated group	Reference Group	*P* Value	Untreated Group	Reference Group	*P* Value
Chronological age, y	12.6 ± 1.9			9.0 ± 3.1		
N-S, mm	65.4 ± 3.2	67.5 ± 2.6	.065	62.7 ± 3.3	63.6 ± 2.8	.511
N-Me, mm	118.2 ± 7.7	123.2 ± 6.0	.067	104.3 ± 11.0	111.0 ± 4.7	.091
N-ANS, mm	53.8 ± 4.6	55.2 ± 3.4	.442	48.2 ± 5.7	49.7 ± 2.7	.437
ANS-Me, mm	67.2 ± 3.5	70.5 ± 4.4	.013*	58.5 ± 6.4	63.3 ± 3.7	.039*
A′-Ptm′, mm	45.6 ± 2.1	47.7 ± 2.4	.006**	42.7 ± 3.7	43.9 ± 2.2	.349
Gn-Cd, mm	108.5 ± 6.1	114.4 ± 5.7	.009**	95.3 ± 9.7	103.5 ± 5.2	.019*
Pog′-Go, mm	70.5 ± 4.3	74.7 ± 4.2	.012*	62.6 ± 6.2	68.5 ± 3.8	.010*
Cd-Go, mm	51.3 ± 3.4	58.1 ± 3.7	<.001***	47.4 ± 5.7	50.1 ± 3.8	.201
∠SNA, °	79.6 ± 3.2	81.5 ± 4.2	.132	77.2 ± 3.5	80.5 ± 3.5	.012*
∠SNB, °	75.6 ± 4.3	77.1 ± 3.8	.344	73.6 ± 2.6	76.2 ± 1.7	.006**
∠ANB, °	4.0 ± 1.6	4.4	NA	3.6 ± 4.1	4.3	NA
Mandibular plane to SN, °	40.7 ± 5.9	40.2 ± 4.6	.824	38.0 ± 5.3	39.4 ± 5.0	.465
Gonial angle, °	128.6 ± 3.6	131.0 ± 5.6	.105	123.1 ± 6.4	128.3 ± 3.7	.025*

[a] N-S indicates anterior cranial base; N-Me, total facial height; N-ANS, upper facial height; ANS-Me, lower facial height; A′-Ptm′, maxillary length; Gn-Cd, mandibular total length; Pog′-Go, mandibular body length; Cd-Go, ramus height; and NA, not available.

* $P < .05$; ** $P < .01$; *** $P < .001$.

Table 3. Linear and Angular Measurements of the Short-term Therapy Group—Mean ± SD of the Cephalometric Measurements of the Growth Hormone Deficiency and the Reference Groups[a,15]

	Boys			Girls		
	Short-term Therapy Group	Reference Group	*P* Value	Short-term Therapy Group	Reference Group	*P* Value
Chronological age, y	11.7 ± 2.9			11.1 ± 2.7		
N-S, mm	64.9 ± 4.0	63.9 ± 2.2	.491	63.9 ± 1.2	63.6 ± 2.8	.608
N-Me, mm	116.0 ± 8.1	111.1 ± 5.3	.099	111.8 ± 7.0	111.0 ± 4.7	.755
N-ANS, mm	52.9 ± 6.3	49.4 ± 3.0	.173	50.9 ± 3.8	49.7 ± 2.7	.422
ANS-Me, mm	65.9 ± 4.0	63.9 ± 3.6	.195	64.1 ± 3.8	63.3 ± 3.7	.597
A′-Ptm′, mm	45.4 ± 3.3	44.8 ± 2.3	.608	45.6 ± 2.8	43.9 ± 2.2	.136
Gn-Cd, mm	105.5 ± 8.2	102.1 ± 4.3	.259	102.3 ± 7.0	103.5 ± 5.2	.645
Pog′-Go, mm	68.2 ± 6.3	68.2 ± 3.3	.99	68.4 ± 4.5	68.5 ± 3.8	.945
Cd-Go, mm	52.2 ± 3.3	49.0 ± 3.7	.018*	50.3 ± 5.5	50.1 ± 3.8	.937
∠SNA, °	79.2 ± 2.5	81.5 ± 4.2	.040*	80.7 ± 2.9	80.5 ± 3.5	.849
∠SNB, °	75.4 ± 4.0	77.1 ± 3.8	.274	75.6 ± 2.2	76.2 ± 1.7	.515
∠ANB, °	3.9 ± 2.2	4.4	NA	5.1 ± 2.9	4.3	NA
Mandibular plane to SN, °	39.4 ± 4.8	40.2 ± 4.6	.667	37.5 ± 4.5	39.4 ± 5.0	.29
Gonial angle, °	126.4 ± 4.4	131.0 ± 5.6	.011*	122.1 ± 4.1	128.3 ± 3.7	<.001***

[a] See Table 2 for definitions of abbreviations.
* $P < .05$; ** $P < .01$; *** $P < .001$.

and A′-Ptm′ was significantly larger than standard values (Table 4).

Analysis of Craniofacial Growth

Characteristics of the craniofacial skeleton. The SD scores of the untreated group were −0.36 (A′-Ptm′), −0.71 (Gn-Cd), −0.86 (Cd-Go), −0.75 (Pog′-Go), −0.53 (N-Me), −0.72 (ANS-Me), and −0.15 (N-S) in comparison with standard values. The SD scores ranged between −0.15 and −0.86.

Anterior cranial base. The mean SD scores of N-S were not significantly different among the three groups: −0.15 (untreated), −0.07 (short-term therapy), and +0.09 (long-term therapy) (Figure 3).

Total facial height. The mean SD scores for N-Me were not significantly different among the three groups: −0.53 (untreated), 0 (short-term therapy), and −0.06 (long-term therapy) (Figure 4).

Upper facial height. The mean SD scores for upper facial height (N-ANS) for the groups were +0.09 (untreated), +0.38 (short-term therapy), and +0.87 (long-term therapy). There was a significant difference between the untreated and long-term therapy groups. The mean SD score tended to increase with the duration of GH therapy (Figure 5).

Lower facial height. The mean SD scores for ANS-Me were not significantly different among the three groups: −0.72 (untreated), −0.14 (short-term therapy), and −0.67 (long-term therapy) (Figure 6).

Maxillary length. The mean SD scores for A′-Ptm′ for the groups were −0.36 (untreated), +0.24 (short-term therapy), and +0.79 (long-term therapy). There was a significant difference between the untreated and long-term therapy groups. The mean SD scores tended to increase with the duration of GH therapy (Figure 7).

Mandibular total length. The mean SD scores for Gn-Cd for the groups were −0.71 (untreated), −0.46 (short-term therapy), and −0.09 (long-term therapy). Although the mean SD scores tended to increase with the duration of GH therapy, there were no significant differences among the three groups (Figure 8).

Mandibular body length. The mean SD scores for Pog′-Go for the groups were −0.75 (untreated), −0.49 (short-term therapy), and −0.23 (long-term therapy). Although the mean SD scores tended to increase with the duration of GH therapy, there were no significant differences among the three groups (Figure 9).

Ramus height. The mean SD scores for Cd-Go for the groups were −0.86 (untreated), −0.39 (short-term therapy), and +0.09 (long-term therapy). There was a significant difference between the untreated and long-term therapy groups, and the mean SD scores tended to increase with the duration of GH therapy (Figure 10).

DISCUSSION

Previous reports that examined the effect of GH therapy on craniofacial growth included non-GHD.[16,17] In Japan, GH therapy was approved only for managing GHD in specific child chronic diseases in 1975 and for managing Turner syndrome accompanied by GHD in 1990.

To examine the effect of GH administration, we studied Japanese boys and girls who were diagnosed with IGHD at puberty. None had a history of brain tumor or central nervous system radiation therapy. Most

Table 4. Linear and Angular Measurements of the Long-term Therapy Group—Mean ± SD of the Cephalometric Measurements of the Growth Hormone Deficiency and the Reference Groups[a,15]

	Boys			Girls		
	Long-term Therapy Group	Reference Group	*P*-Value	Long-term Therapy Group	Reference Group	*P*-Value
Chronological age, y	12.1 ± 3.3			12.9 ± 2.4		
N-S, mm	66.2 ± 3.2	67.5 ± 2.6	.166	63.7 ± 2.5	64.9 ± 3.0	.215
N-Me, mm	115.8 ± 11.1	123.2 ± 6.0	.018*	114.5 ± 7.1	117.4 ± 4.6	.248
N-ANS, mm	54.6 ± 5.8	55.1 ± 3.4	.766	53.1 ± 3.8	51.5 ± 2.7	.216
ANS-Me, mm	64.1 ± 6.5	70.5 ± 4.4	.001**	64.0 ± 4.3	68.0 ± 3.7	.010*
A′-Ptm′, mm	47.2 ± 2.9	47.7 ± 2.4	.553	46.6 ± 2.3	44.7 ± 1.7	.020*
Gn-Cd, mm	107.2 ± 9.2	114.4 ± 5.7	.007**	107.2 ± 6.4	110.6 ± 4.2	.126
Pog′-Go, mm	69.4 ± 5.3	74.7 ± 4.2	.001**	70.9 ± 4.1	72.4 ± 3.2	.295
Cd-Go, mm	54.7 ± 5.4	58.1 ± 3.7	.034*	52.4 ± 4.2	55.5 ± 3.5	.043*
∠SNA, °	79.8 ± 3.0	81.5 ± 4.2	.105	81.5 ± 3.7	80.5 ± 3.5	.447
∠SNB, °	76.0 ± 3.9	77.1 ± 3.8	.345	77.2 ± 4.8	76.2 ± 1.7	.542
∠ANB, °	3.8 ± 2.7	4.4	NA	4.3 ± 2.8	4.3	NA
Mandibular plane to SN, °	35.9 ± 5.5	40.2 ± 4.6	.008**	38.2 ± 4.6	39.4 ± 5.0	.472
Gonial angle, °	124.0 ± 4.5	131.0 ± 5.6	<.001***	124.1 ± 5.4	128.3 ± 3.7	.024*

[a] See Table 2 for definitions of abbreviations.
* $P < .05$; ** $P < .01$; *** $P < .001$.

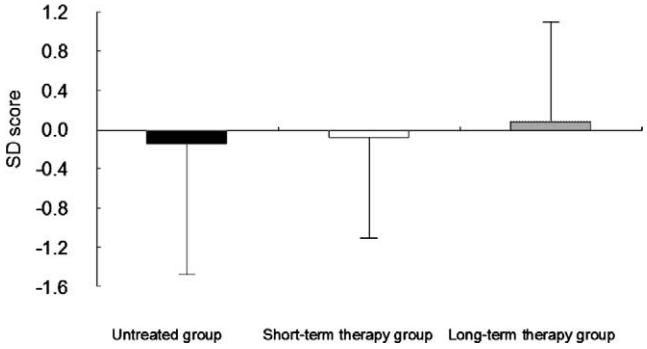

Figure 3. Anterior cranial base (N-S). There were no significant differences among the three groups.

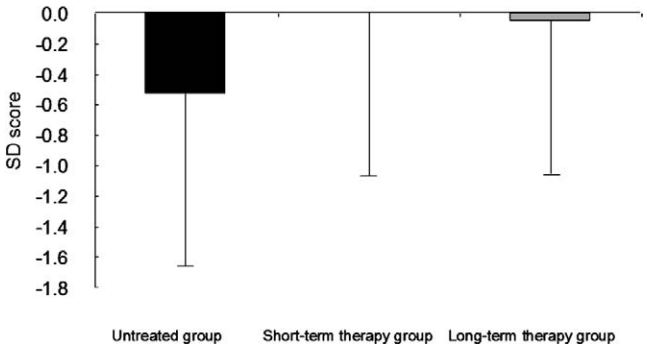

Figure 4. Total facial height (N-Me). There were no significant differences among the three groups.

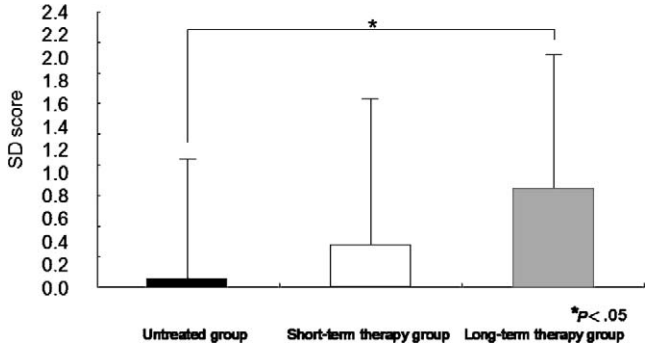

Figure 5. Upper facial height (N-ANS). There was a significant difference between the untreated and long-term therapy groups ($P < .05$).

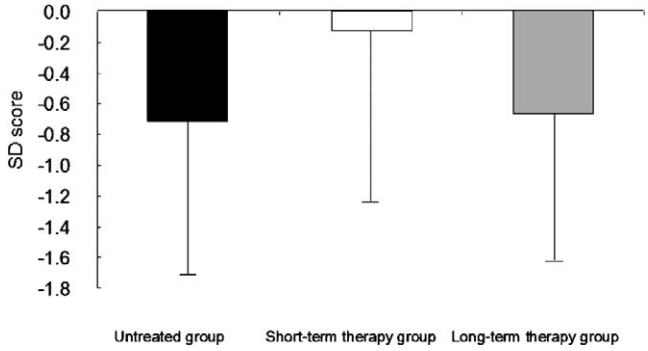

Figure 6. Lower facial height (ANS-Me). There were no significant differences among the three groups.

IGHD occurs during infancy or by age 2 years,[18] whereas organic GHD does not occur at a consistent age. Turner syndrome was also excluded, even if there was a GHD, because it is a disease caused by a single sex chromosome (XO) that affects only females.[19]

In this study, the SD scores were compared with standard values. The physique of modern Japanese children has changed rapidly. In 1948, the mean height was 160.6 cm for a 17-year-old Japanese boy and 152.1 cm for a 17-year-old Japanese girl. Today,

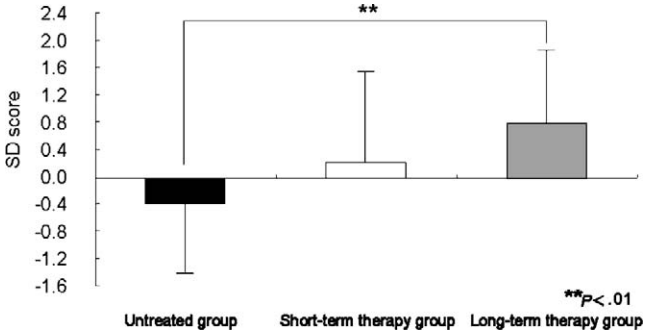

Figure 7. Maxillary length (A′-Ptm′). There was a significant difference between the untreated and long-term therapy groups ($P < .01$).

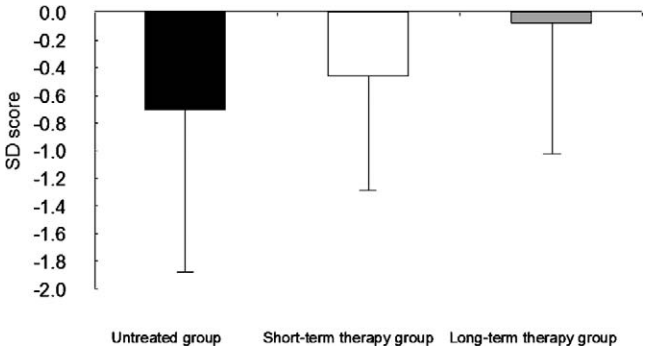

Figure 8. Mandibular total length (Gn-Cd). The mean scores tended to increase with the duration of growth hormone therapy.

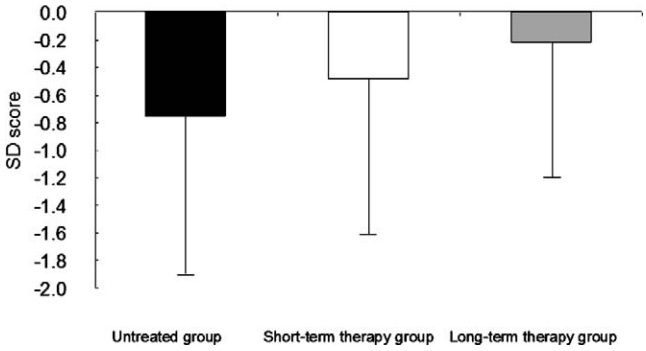

Figure 9. Mandibular body length (Pog′-Go). The mean scores tended to increase with the duration of growth hormone therapy.

boys are approximately 10 cm taller and girls are approximately 6 cm taller.[20] Compared with the standard value of each cephalometric measurement at every age group, the standard values reported in 1995[21] were significantly greater than the standard values reported by Sakamoto et al[15] in 1960s. Changes in the size, morphology, and growth of the maxilla have resulted from the rapid development of the physique of modern Japanese children. Therefore, we must use standard values of the craniofacial skeleton according to recent data. The standard values reported by the Japanese Society of Pediatric Dentistry[21] in 1995 did

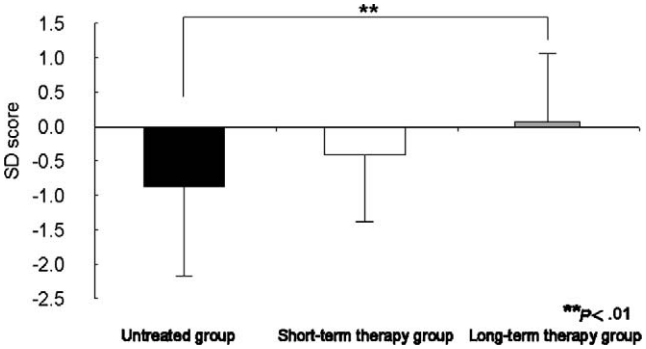

Figure 10. Ramus height (Cd-Go). There was a significant difference between the untreated and long-term therapy groups ($P < .01$).

not include measurements of the mandibular condyle, making it difficult to accurately determine Pog′-Go and Cd-Go. Therefore, we used the standard values reported by Sakamoto et al[15] in 1963 and converted each subject's measurements to SD scores.

Characteristics of the Craniofacial Skeleton in IGHD

There are few reports on the characteristics of craniofacial growth in untreated IGHD. Cantu et al[9] compared treated and untreated groups, whereas other authors[4,5,8] examined treated and untreated groups without discrimination.

With respect to the N-S length, Poole et al[7] reported that it was not reduced, whereas Cantu et al[9] reported that it was reduced −0.15 SD compared with the standard value. There are many areas of cartilaginous growth at the cranial base. Although GH is reported to accelerate cartilaginous growth,[2,22] we found little evidence of this.

Studies have reported that the A′-Ptm′ is reduced significantly[5] and to the same degree as the mandible.[6,7] Although the maxilla is often posterior, the A′-Ptm′ is not reduced more than that of the mandible.[8,9] In this study, we obtained a value of −0.36 SD for A′-Ptm′. With respect to the mandible, the SD scores in the untreated group were −0.71 (Gn-Cd), −0.86 (Cd-Go), and −0.72 (ANS-Me), which were all smaller than the respective standard values. This concurs with published reports.[5–9]

Effect of GH Therapy on Craniofacial Growth

After the administration of GH, the SD scores for the N-ANS, A′-P+m′, and Cd-Go increased significantly. GH therapy accelerates cartilage growth.[2,22] Consequently, intramembranous bone growth, including the suture, as well as cartilage growth may accelerate. Accelerated cartilage growth was detected by the Cd-Go, which is a vertical component. This may be related to GH, which plays an important role in longitudinal bone

growth.[2] GH therapy had started at a younger age among those in the long-term therapy group than among those in the untreated or short-term therapy groups. We postulate that the GHD in the long-term therapy group was more severe than in the other groups. Regarding the Gn-Cd and Pog′-Go, there were no significant differences among the three groups. However, the mean SD scores tended to increase with the duration of therapy. It is thought that the differences were not significant because the GHD was more serious in the long-term therapy group than in the other groups.

Rongen-Westerlaken et al[23] reported that the gonial angle increased because the Cd-Go increased significantly, thereby increasing the ANS-Me significantly. In this study, however, no increase was detected in the ANS-Me. Therefore, the cases with severe vertical problems may have existed before GH therapy began in the long-term therapy group, as our data represent a cross-sectional sample. Similarly, the mean SD score for N-Me in the long-term therapy group is thought to be smaller than that in the short-term therapy group for the same reason. This needs to be examined in a longitudinal sample.

For the N-ANS, A′-Ptm′, and Cd-Go, the SD scores of the long-term therapy group were significantly greater than those of the untreated group. It is thought that the significant difference occurred because GH therapy induces the greatest amount of catch-up growth within the first 1 to 2 years.

These findings suggest that GH accelerates catch-up growth of the cranial skeleton and thus improves occlusion and the facial profile. Growth factors such as GH and IGF-α may be useful for correcting the Class II pattern of the retrusive mandible in orthodontics.

Future Research

Body height at puberty is reported to be correlated with final body height.[10] Therefore, to succeed with GH therapy, we need to promote growth before puberty so that the body height is similar to that of a normal child before puberty. This may also be applicable to craniofacial growth, especially at the sites of cartilaginous growth. In this study, we measured the length of the maxilla, which undergoes intramembranous bone growth. Further research needs to examine other parameters, such as the calvarial length.

We examined the effect of GH on craniofacial growth in a cross-sectional sample to conduct a statistical examination with as much data as possible. When using cross-sectional samples, the craniofacial morphology in untreated GH and the degree of GHD are unknown. The synchondroses in the cranial base complete earlier, and there is differential growth of the craniofacial skeleton. The mean age of bone of samples in this study was from 9.5 to 11.6 years. Some of the girls may have started their adolescent growth spurt, and there may have been other factors to affect the results except for GH. We plan to continue with a longitudinal study to examine the effects of GH on craniofacial growth in GHD for patients treated with GH at a younger age.

CONCLUSION

- Children who received long-term GH therapy (more than 2 years) showed increased growth of the craniofacial skeleton, especially the maxilla and mandibular ramus.
- These findings suggest that GH accelerates craniofacial development, which improves occlusion and the facial profile.

ACKNOWLEDGMENTS

We are grateful to Dr. Kunihiko Hanew, Dr. Takako Ogata and Dr. Toshinori Mito for their valuable advice.

REFERENCES

1. Brasel JA, Blizzard RM. *Textbook of Endocrinology.* 5th ed. Philadelphia, Pa: WB Sauders; 1974.
2. Ohlsson C, Bengtsson BA, Isaksson OG, Andreassen TT, Slootweg MC. Growth hormone and bone. *Endocr Rev.* 1998;19:55–79.
3. Rank MB, Bierich JR. Treatment of growth hormone deficiency. *Clin Endocr Metab.* 1986;15:495–510.
4. Bevis RR, Hayles AB, Isaacson RJ, Sather AH. Facial growth response to human growth hormone in hypopituitary dwarfs. *Angle Orthod.* 1977;47:193–205.
5. Konfino R, Pertzelan A, Laron Z. Cephalometric measurements of familial dwarfism and high plasma immunoreactive growth hormone. *Am J Orthod.* 1975;68:196–201.
6. Takano K, Ogiuchi H, Hizuka N, Sangu Y, Shizume K. Oromaxillofacial development in patients with GH deficiency and in normal short children. *Endocrinol Jpn.* 1986;33:655–664.
7. Poole AE, Greene IM, Buschang PH. The effect of growth hormone therapy on longitudinal growth of the oral facial structures in children. *Prog Clin Biol Res.* 1982;101:499–516.
8. Pirinen S, Majurin A, Lenko HL, Koski K. Craniofacial features in patients with deficient and excessive growth hormone. *J Craniofac Genet Dev Biol.* 1994;14:144–152.
9. Cantu G, Buschang PH, Gonzalez JL. Differential growth and maturation in idiopathic growth-hormone-deficient children. *Eur J Orthod.* 1997;19:131–139.
10. Tanaka T, Yoshizawa A, Tanae A, Hibi I, Shizume K. Relationships between puberty and growth at adolescence in growth-hormone-deficient males: effect of growth hormone and of associated gonadal suppression therapy. *Horm Res.* 1990;33:102–105.
11. Milner RD, Russell-Fraser T, Brook CG, et al. Experience with human growth hormone in Great Britain: the report of the MRC Working Party. *Clin Endocrinol (Oxf).* 1979;11:15–38.
12. Job JC. Results of long-term growth hormone replacement therapy in children: when and how to treat? *Horm Res.* 1990;33:69–76.

13. Murata M, Matsuo N, Tanaka T, et al. *Atlas of Standard Bone Maturation for Japanese—Based on TW2 Method* [in Japanese]. Tokyo: Kanehara Shuppan; 1993:57–81.
14. Suwa S, Tachibana K, Maesaka H, Tanaka T, Yokoya S. Longitudinal standards for height and height velocity for Japanese children from birth to maturity. *Clin Pediatr Endocrinol.* 1992;1:5–13.
15. Sakamoto T, Miura F, Iizuka T. Linear analyses on the development changes of dentofacial complex of Japanese by means of roentgenographic cephalometry [in Japanese]. *J Stomatol Soc.* 1963;30:169–182.
16. van Erum R, Mulier M, Carels C, Verbeke G, de Zegher F. Craniofacial growth in short children born small for gestational age: effect of growth hormone treatment. *J Dent Res.* 1997;76:1579–1586.
17. Kjellberg H, Beiring M, Albertsson W. Craniofacial morphology, dental occlusion, tooth eruption, and dental maturity in boys of short stature with or without growth hormone deficiency. *Eur J Oral Sci.* 2000;108:359–367.
18. Brook CGD, Hindmarsh PC, Smith PJ, Stanhope R. Clinical features and investigation of growth hormone deficiency. *Clin Edocrinol Metab.* 1986;15:479–493.
19. Wilson JD, Foster DW. *Williams Textbook of Endocrinology.* 8th ed. Philadelphia, Pa: WB Saunders; 1992.
20. Ministry of Education, Culture, Sports, Science and Technology. *Annual Report of School Health Statistics* [in Japanese]. Tokyo, Japan: Printing Office, Ministry of Finance; 1996.
21. Japanese Society of Pediatric Dentistry. Study of standard value of dentofacial complex of Japanese children by means of roentgenographic cephalometry [in Japanese]. *Jpn J Pedodont.* 1995;33:659–696.
22. Isaksson OG, Lindahl A, Nilsson A, Isgaard J. Mechanism of the stimulatory effect of growth hormone on longitudinal bone growth. *Endocr Rev.* 1987;8:426–438.
23. Rongen-Westerlaken C, vd Born E, Prahl-Andersen B, et al. Effect of growth hormone treatment on craniofacial growth in Turner's syndrome. *Acta Paediatr.* 1993;82:364–368.