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ORIGINAL ARTICLE

Effect of growth hormone treatment on craniofacial growth in children: Idiopathic short stature versus growth hormone deficiency

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KEYWORDS
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Background/purpose: Few studies have evaluated craniofacial growth in boys and girls with idiopathic short stature (ISS) during growth hormone (GH) treatment. The aim of this study was to evaluate the effect of GH treatment on craniofacial growth in children with ISS, compared with those with growth hormone deficiency (GHD).
Methods: This study included 36 children (mean age, 11.3 ± 1.8 years) who were treated with GH consecutively. Lateral cephalograms were analyzed before and 2 years after start of GH treatment.
Results: There were no significant differences in age and sex between ISS and GHD groups and the reference group from semilongitudinal study (10 boys and 8 girls from each group). Before treatment, girls with ISS showed a skeletal Class II facial profile compared with the GHD and reference groups ($p = 0.003$). During GH treatment, the amount of maxillary length increased beyond norm in the ISS and GHD groups in boys ($p = 0.035$) > 3 standard deviation score (SDS). Meanwhile, mandibular ramus height ($p = 0.001$), corpus length, and total mandibular length ($p = 0.007$ for both) increased more in girls with ISS than in girls with GHD. Lower and total anterior facial heights increased more in girls with ISS than in girls with GHD ($p = 0.021$ and $p = 0.007$, respectively), > 7–11 SDS.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: GH should be administered carefully when treating girls with ISS, because GH treatment has great effects on vertical overgrowth of the mandible and can result in longer face.

Introduction

Growth disorders, associated with growth hormone (GH) in children, include growth hormone deficiency (GHD), idiopathic short stature (ISS), Noonan syndrome, Prader–Willi syndrome, and Turner syndrome.[1,2] Among these, ISS is defined as a height less than third percentile or two SDs (standard deviations) for age, sex, and population without evidence of nutritional, systemic chronic disease, endocrine, and chromosomal abnormalities.[3,4] The cause of ISS may be gene mutations and deletions in the SHOX gene for children, the prevalence has been estimated at 1–5%.[4,5] In addition, a karyotype should be considered in girls with no underlying specific cause of ISS to rule out Turner syndrome.[4]

As children with ISS often remain short in adult life, in 2003, the United States (US) Food and Drug Administration (FDA) approved use of GH for treatment of ISS in children whose presenting height is < -2.25 SDs for age, sex, and that height in adult life is expected to be below normal.[6] Several studies concluded that GH therapy can result in higher adult heights in some treated children.[7–9] The consensus was that the mean increase in adult height with GH therapy is 3.5–7.5 cm.[10]

However, to the best of our knowledge, few studies have evaluated craniofacial growth in ISS during GH treatment. Kjellberg et al[11] reported an enhancement of overall craniofacial growth in boys with ISS and the mandibular body length and anterior facial height of the boys treated GH were greater at the end of treatment compared with those in the reference group. However, that study had a limitation that girls with ISS were not included as subjects because most children seeking GH treatment were boys. Grimberg et al[12] reported that sex difference in short stature referrals may miss the diagnosis and treatment of diseases in girls whose growth problems are undervalued. Therefore, growth change of the craniofacial complex in girls with ISS should be determined during GH treatment.

The aim of this study was to evaluate the effect of GH treatment on craniofacial growth in children with ISS, compared with those with GHD. The investigators hypothesize that craniofacial growth pattern is significantly different between children, especially girls with ISS and those with GHD 2 years after GH treatment.

Methods

Study design/sample

The study population comprised 40 children who presented for evaluation and management of short statue with ISS or with GHD who underwent GH treatment from 2006 to 2012 at the Department of Pediatrics, Yeungnam University Hospital, Daegu, Korea.

Inclusion criteria were as follows: chronological age > 5 years old; less than third percentile or two SDs below the normal mean height for subjects of a similar age and sex or growth velocity according to the Korean population;[13] no history of GH treatment within 6 months; prepubertal stage according to Tanner stage criteria based on testicular volume in boys and breast development in girls.

Among a total of 40 children whose caregivers agreed with taking radiographs for measurements of the cephalometics, four dropped out (two from each group) 1 year after GH treatment because two refused to continue the treatment and two were lost to follow-up, 18 patients were diagnosed with idiopathic GHD and 18 patients were diagnosed with ISS. The clinical diagnosis of GHD was defined by height less than the third percentile and peak GH response < 10 ng/mL after one of three growth hormone stimulation tests using insulin, L-dopa, and clonidine. ISS was defined when patients had short stature less than third percentile without evidence of a systemic disease, nutritional, psychological of chromosomal disorder, and peak GH response more than 10 ng/mL after growth hormone stimulation tests. The patients were injected with 0.23 mg of recombinant growth hormone (rGH) /kg/week (mean dose), six times weekly for 2 years. The study protocol conforms to the Declaration of Helsinki and was approved by the Institutional Review Board of Yeungnam University Hospital, Daegu, Korea.

Reference group

The reference group consisted of healthy children with Class I molar relationships and normal occlusion selected from elementary schools in Daegu. Semilongitudinal growth study data traced and surveyed for 10 years from May 1983 by the Department of Orthodontics, Kyungpook National University Hospital, Daegu, Korea, were used. Eighteen children data were selected to fit those of the short-statured children.

Cephalometric analysis

Patients and their parents were asked if they would agree to allow measurement of their craniofacial structure by an orthodontist at the Department of Dentistry, Yeungnam University Hospital, Daegu, Korea, before undergoing GH treatment. For those who agreed, a written informed consent was obtained from each patient and parents before GH treatment. Craniofacial growth changes were evaluated using lateral cephalograms obtained before (T0) and 2 years (T1) after start of GH treatment. The lateral cephalograms were digitized using V-ceph 5.5 (Osstem, Seoul, Korea) by an observer who was blinded to the patients' clinical status. Based on the Pancherz's cephalometric method,[14] all reference planes were transferred from the T0 to T1 cephalograms according to the S (sella)-N (nasion) plane superimposition at S. This study identified nine linear and seven angular cephalometric measurements to evaluate the change of the craniofacial complex in each group during GH treatment (Figure 1).

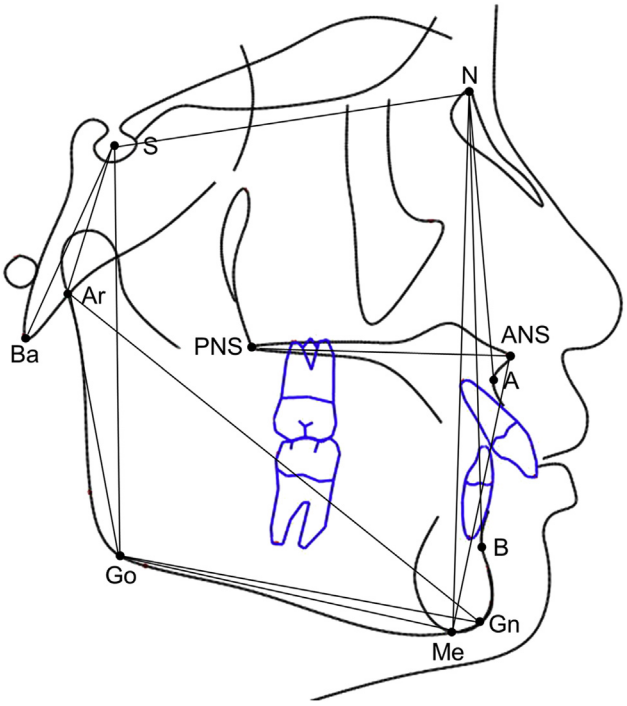


Figure 1 Cephalometric reference points, lengths, and angles. A = point A; ANB, maxilla-mandible relation; ANS = anterior nasal spine; ANS-Me = lower anterior facial height; ANS-PNS = maxillary length; Ar = articulare; Ar-Gn = total mandibular length; Ar-Go = mandibular ramus height; Ar-Go-Me = gonial angle; B = point B; Ba = basion; Gn = gnathion; Go = gonion; Go-Gn = mandibular corpus length; Me = menton; N = nasion; N-Me = total anterior facial height; N-S = anterior cranial base length; N-S-Ar = cranial base angle; PNS = posterior nasal spine; S = sella; S-Ba = posterior cranial base length; S-Go = posterior facial height; SNA = maxilla-cranial base relation; SN-ArGo = ramal angle; SNB = mandible-cranial base relation; SN-GoMe = mandibular plane angle.

Reproducibility

Reproducibility was determined by comparing measurements obtained during original examinations with those obtained during repeated examinations. All measurements were repeated by the same observer after 2 weeks. The method error was calculated using the intraclass correlation coefficient (ICC), which was > 0.90 for all linear and angular cephalometric measurements used in this study.

Statistical analysis

All statistical analyses were performed using IBM SPSS software, version 21.0 (IBM Korea Inc., Seoul, Korea) for Windows. In order to verify the normality of data distribution, the Shapiro—Wilk test was applied. Descriptive statistics, including means and standard deviations, were used to describe each variable analyzed in the study. Differences in patients' heights and weights between groups were analyzed using the Kruskal—Wallis test.

The Kruskal—Wallis test with Bonferroni correction was used for comparison of cephalometric measurements in each boy or girl between groups before (T0) and 2 years after start of GH treatment (T1). All variables were converted standard deviation score (SDS) using the reference group for comparison of craniofacial growth changes (T1—T0) during GH treatment between groups, using the Mann—Whitney U test. SDS was calculated as measurement minus mean of the reference group divided by standard deviation of the reference group. Thus, a positive standard score indicates a datum above the mean, while a negative standard score indicates a datum below the mean.

Correlations between craniofacial growth changes, age, sex, and groups (the GHD and the ISS) were evaluated using Spearman's rank correlation coefficients. With regard to the strengths of the correlations, $r > 0.40$ indicated a moderate-to-strong correlation and $r < 0.40$ indicated a

Table 1 Subjects characteristics.

		GHD group (n = 18)	ISS group (n = 18)	Reference group (n = 18)	P value
Sex n (%)					NS
Boys		10 (55.6)	10 (55.6)	10 (55.6)	
Girls		8 (44.4)	8 (44.4)	8 (44.4)	
Chronological age (mean ± SD, year)		11.3 ± 1.9	11.2 ± 1.8	10.8 ± 1.8	NS
(Range)		(9—15)	(9—15)	(9—15)	
Body height (median, cm)					
Boys	Before GH treatment	128.7	132.4	139.4	< 0.001
	At 2 years after start of GH treatment	148.8	150.5	151.8	NS
Girls	Before GH treatment	124.4	125.7	139.9	< 0.001
	At 2 years after start of GH treatment	143.6	150.8	152.7	NS
Body weight (median, kg)					
Boys	Before GH treatment	29.4	33.2	35.5	< 0.001
	At 2 years after start of GH treatment	42.1	52	45.5	NS
Girls	Before GH treatment	24.1	25.0	34.7	< 0.001
	At 2 years after start of GH treatment	36.6	40.6	43.8	NS

GHD = growth hormone-deficient; GH = growth hormone; ISS = idiopathic short stature; NS, not statistically significant; SD = standard deviation.

Table 2 Mean and standard deviation of cephalometric measurements between groups before growth hormone treatment.

Variables	Boys				*Post hoc*	Girls				*Post hoc*
	GHD group[a]	ISS group[b]	Reference group[c]	*p*		GHD group[a]	ISS group[b]	Reference group[c]	*P*	
Linear measurements (mm)										
Anterior cranial base length (N-S)	64.23 ± 1.98	65.90 ± 3.06	68.60 ± 1.35	0.002	a < c	63.75 ± 1.36	65.81 ± 1.51	68.19 ± 1.79	0.001	a < c
Posterior cranial base length (S-Ba)	44.17 ± 2.61	46.20 ± 2.53	49.20 ± 2.96	0.004	a < c	44.50 ± 3.22	43.63 ± 0.74	43.63 ± 2.74	0.699	
S-Ba/N-S (%)	68.73 ± 2.51	70.16 ± 3.47	71.67 ± 3.04	0.091		69.75 ± 3.97	66.30 ± 1.10	63.93 ± 2.42	0.007	a > c
Maxillary length (ANS-PNS)	44.10 ± 3.29	46.60 ± 4.27	47.00 ± 3.62	0.103		44.75 ± 2.36	42.94 ± 0.62	46.38 ± 1.58	0.004	b < c
Mandibular ramus height (Ar-Go)	38.55 ± 3.02	39.40 ± 2.37	43.70 ± 4.54	0.012	a < c	36.13 ± 4.36	36.81 ± 4.88	42.49 ± 2.23	0.010	a < c
Mandibular corpus length (Go-Gn)	68.50 ± 4.63	73.65 ± 1.63	74.60 ± 4.14	0.008	a < b, a < c	70.38 ± 4.30	68.88 ± 1.55	73.69 ± 2.96	0.011	
Ar-Go/Go-Gn (%)	56.50 ± 5.90	53.52 ± 3.40	58.47 ± 3.29	0.030		51.18 ± 3.22	53.33 ± 5.97	57.64 ± 1.00	0.009	a < c
Total mandibular length (Ar-Gn)	97.00 ± 5.52	103.30 ± 4.79	102.1 ± 5.26	0.026		98.13 ± 3.76	98.13 ± 2.59	99.38 ± 6.52	0.647	
Lower anterior facial height (ANS-Me)	65.65 ± 3.50	67.60 ± 3.61	65.13 ± 3.19	0.302		63.88 ± 2.22	62.63 ± 0.52	63.75 ± 4.41	0.570	
Anterior facial height (N-Me)	114.85 ± 4.70	118.50 ± 6.94	118.71 ± 5.35	0.159		113.44 ± 1.32	113.00 ± 1.51	115.06 ± 6.06	0.901	
Posterior facial height (S-Go)	67.35 ± 5.07	68.05 ± 7.11	74.41 ± 6.82	0.088		68.44 ± 4.44	66.81 ± 2.09	70.88 ± 2.89	0.113	
Angular measurements (°)										
Cranial base angle (N-S-Ar)	127.90 ± 4.23	125.95 ± 3.75	122.10 ± 1.85	0.004	a > c	124.13 ± 4.35	125.81 ± 1.81	127.19 ± 1.81	0.079	
Ramal angle (SN-ArGo)	88.25 ± 3.62	87.20 ± 2.26	86.2 ± 3.44	0.123		87.56 ± 4.69	86.38 ± 1.55	86.88 ± 1.55	0.284	
Gonial angle (Ar-Go-Me)	127.50 ± 3.95	125.00 ± 1.37	124.20 ± 2.66	0.415		127.25 ± 3.22	126.56 ± 0.78	127.38 ± 8.15	0.917	
Mandibular plane angle (SN-GoMe)	35.15 ± 2.31	36.15 ± 3.73	33.20 ± 0.71	0.010		36.38 ± 3.37	37.13 ± 2.39	36.56 ± 8.50	0.573	
Maxilla-cranial base relation (SNA)	79.00 ± 2.87	80.65 ± 3.61	79.75 ± 1.30	0.388		80.75 ± 2.60	81.13 ± 1.77	78.31 ± 0.70	0.011	
Mandible-cranial base relation (SNB)	74.70 ± 3.68	76.95 ± 3.26	77.30 ± 1.72	0.178		77.50 ± 3.74	76.00 ± 1.69	75.25 ± 1.46	0.500	
Maxilla-mandible relation (ANB)	4.30 ± 1.44	3.60 ± 1.20	2.40 ± 0.77	0.018	a > c	3.19 ± 1.51	5.13 ± 0.52	3.06 ± 1.29	0.003	a < b, b > c

P values were calculated by the Kruskal-Wallis test with Bonferroni correction.
GHD = growth hormone-deficient; ISS = idiopathic short stature.

weak correlation. A p value ≤ 0.05 or less was considered significant.

Results

Thirty six patients (20 boys and 16 girls; mean age, 11.3 ± 1.8 years) fulfilled the inclusion criteria for this study (Table 1). There were no significant differences in age and sex between ISS, GHD, and the reference groups (10 boys and 8 girls from each group). Body heights and weights of boys and girls were lower in the GHD and ISS groups compared with the reference group before GH treatment ($p < 0.001$). After GH treatment, body heights and weights in children with GHD and those with ISS were almost the same as those in children in the reference group, proving the effect of 2 years of GH treatment in children with both idiopathic GHD and ISS.

Before GH treatment, boys with GHD had shorter anterior and posterior cranial base lengths ($p = 0.002$ and $p = 0.004$, respectively) and mandibular ramus height and corpus length ($p = 0.012$ and $p = 0.008$, respectively) than those in the reference group (Table 2). In addition, boys with GHD had greater maxilla-mandible relation (ANB) than those with reference group ($p = 0.018$), indicating that boys with GHD had skeletal Class II tendency compared with boys with the reference group before GH treatment. Likewise, girls with GHD had shorter anterior cranial base length ($p = 0.001$) and mandibular ramus height ($p = 0.010$) than those in the reference group (Table 2). Girls with ISS had greater ANB ($p = 0.003$) than those in the GHD and reference groups, indicating that girls in the ISS group had skeletal Class II facial profile compared with the GHD and reference groups before GH treatment.

During GH treatment, most measurements improved toward norm in boys with GHD and those with ISS (Table 3). Significantly accelerated growth beyond norm was observed in the two groups for maxillary length over 3 SDS ($p = 0.035$). There were no significant differences in the amounts of change in angular measurements between the groups. The amounts of increase in posterior cranial base length was greater in girls with GHD than in girls with ISS ($p = 0.021$). Mandibular ramus height ($p = 0.001$), corpus length, and total mandibular length ($p = 0.007$ for both) increased more in girls with ISS than in girls with GHD, over 3–6 SDS (Figure 2). As a result, lower and total anterior facial heights increased significantly more in girls with ISS than in girls with GHD ($p = 0.021$ and $p = 0.007$, respectively), over 7–11 SDS.

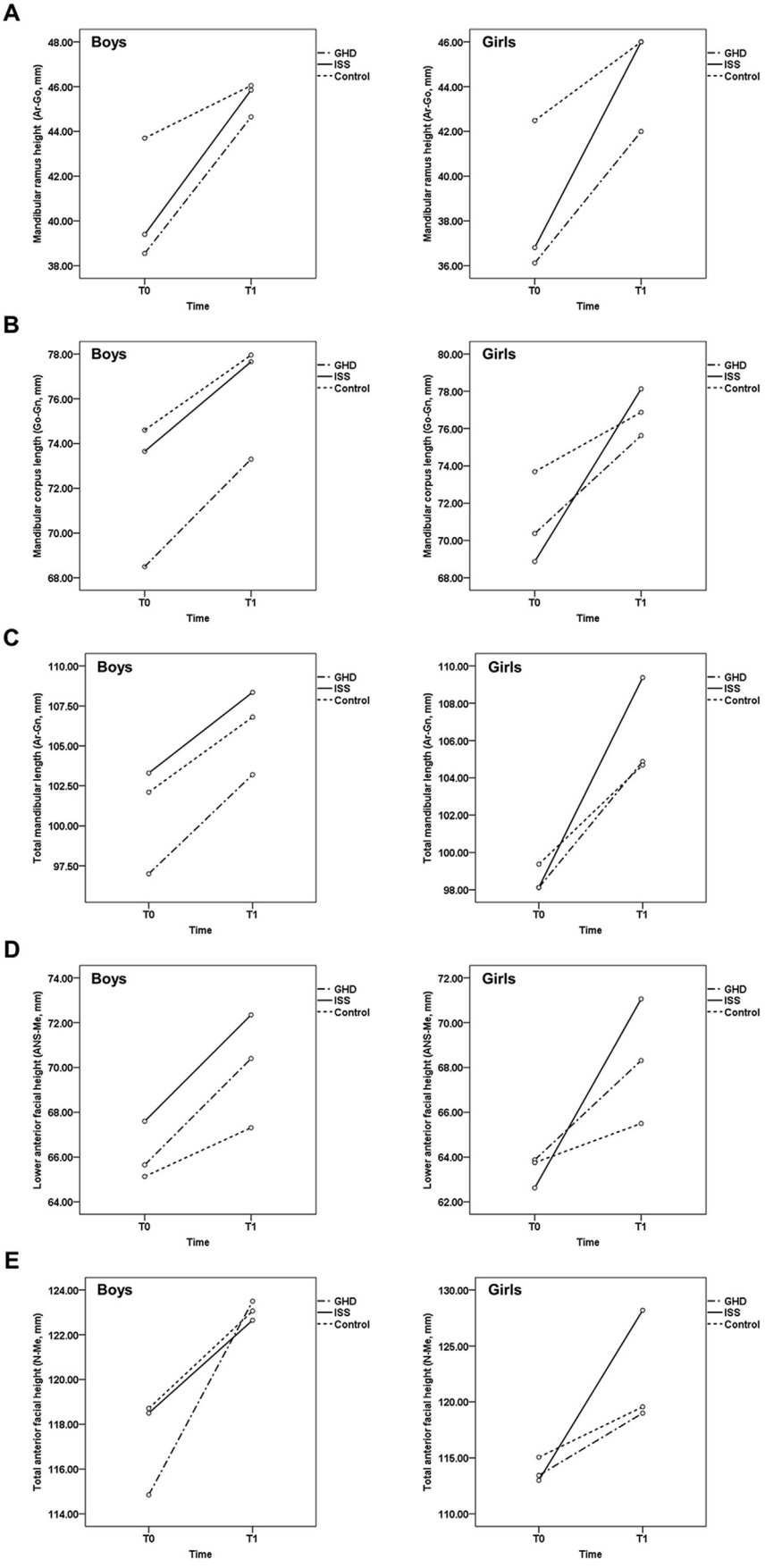
Two years after GH treatment, the sagittal skeletal relationship improved significantly in boys with GHD and those with ISS, compared with boys in the reference group (Table 4). Lower and total anterior facial heights were significantly greater in girls in the ISS group than in girls in the reference groups ($p = 0.026$ and $p = 0.007$, respectively). Posterior facial heights were greater in girls with ISS compared with those in the reference group ($p = 0.007$).

With younger age at the start of GH treatment, the amounts of increase in posterior cranial base length (r,

Table 3 Changes of standard deviation scores (SDS) of transformed outcome variables during growth hormone treatment between groups.

Variables	Boys			Girls		
	GHD group	ISS group	p	GHD group	ISS group	p
Linear measurements (mm)						
Anterior cranial base length (N-S)	3.42 ± 1.12	2.67 ± 0.98	0.063	4.44 ± 2.51	2.12 ± 0.30	0.050
Posterior cranial base length (S-Ba)	1.51 ± 1.44	1.45 ± 1.07	0.853	4.40 ± 2.15	1.97 ± 1.23	0.021
Maxillary length (ANS-PNS)	5.47 ± 3.21	3.14 ± 2.10	0.035	1.55 ± 1.37	2.17 ± 0.51	0.328
Mandibular ramus height (Ar-Go)	1.45 ± 0.73	1.59 ± 0.74	1.000	1.97 ± 0.70	4.73 ± 2.12	0.001
Mandibular corpus length (Go-Gn)	1.45 ± 2.25	0.65 ± 3.00	0.529	2.24 ± 3.26	6.59 ± 1.13	0.007
Total mandibular length (Ar-Gn)	0.94 ± 1.99	0.22 ± 2.43	0.315	0.89 ± 2.37	3.67 ± 0.64	0.007
Lower anterior facial height (ANS-Me)	1.80 ± 0.72	1.80 ± 2.13	0.436	3.02 ± 2.71	7.51 ± 3.86	0.021
Total anterior facial height (N-Me)	2.95 ± 1.79	−0.14 ± 5.46	0.023	1.11 ± 2.53	11.13 ± 7.66	0.007
Posterior facial height (S-Go)	3.57 ± 1.71	1.29 ± 3.13	0.029	3.76 ± 2.45	4.90 ± 1.06	0.382
Angular measurements (°)						
Cranial base angle (N-S-Ar)	1.31 ± 3.56	1.85 ± 4.07	0.853	0.35 ± 1.09	0.58 ± 0.73	0.645
Ramal angle (SN-ArGo)	−0.63 ± 1.45	−1.31 ± 1.34	0.218	−0.06 ± 1.94	0.70 ± 0.22	0.328
Gonial angle (Ar-Go-Me)	−1.46 ± 5.53	0.47 ± 3.85	0.436	−0.17 ± 2.01	0.19 ± 1.50	0.959
Mandibular plane angle (SN-GoMe)	−1.20 ± 2.31	−1.48 ± 2.03	0.796	−0.82 ± 0.99	−0.21 ± 0.18	0.234
Maxilla-cranial base relation (SNA)	−1.05 ± 2.06	2.12 ± 9.52	0.684	−0.38 ± 0.40	−0.41 ± 0.28	0.959
Mandible-cranial base relation (SNB)	−0.01 ± 0.89	0.95 ± 3.98	0.684	0.27 ± 2.23	0.82 ± 0.77	0.382
Maxilla-mandible relation (ANB)	−0.58 ± 1.26	0.10 ± 1.76	0.143	−0.53 ± 0.45	−0.75 ± 0.51	0.382

P values were calculated by the Mann–Whitney U-test.
GHD = growth hormone-deficient; ISS = idiopathic short stature.


A
Boys
Girls
Mandibular ramus height (Ar-Go, mm)
B
Mandibular corpus length (Go-Gn, mm)
C
Total mandibular length (Ar-Gn, mm)
D
Lower anterior facial height (ANS-Me, mm)
E
Total anterior facial height (N-Me, mm)
Time
T0
T1
GHD
ISS
Control

−0.451; $p < 0.01$), maxillary length (r, −0.541; $p < 0.001$), and total mandibular length (r, −0.353; $p < 0.05$) increased during GH treatment (Table 5). The amounts of mandibular corpus length and total mandibular length increased more in girls than in boys by GH (r, 0.442−0.446; $p < 0.01$ for both). By contrast, anterior cranial base length increased more in boys than in girls (r, −0.636; $p < 0.001$). The mandibular ramus height increased more in children with ISS than in those with GHD (r, 0.376; $p < 0.05$). Anterior and posterior cranial base lengths increased more in children with GHD than in those with ISS during GH treatment (r, −0.349−−0.334; $p < 0.05$ for both).

Discussion

The aim of this study was to evaluate the effect of GH on craniofacial growth in children with ISS, compared with those with GHD. The hypothesis was that craniofacial growth pattern is significantly different between girls with ISS and those with GHD. The results showed that there were no significant intergroup differences in boys after GH treatment (Table 4). However, the amount of the mandibular growth was significantly greater in girls with ISS than in those with GHD during GH treatment. As a result, anterior facial height in girls with ISS was greater than those in the reference group at 2 years after start of GH treatment.

Kjellberg et al[11] reported that a prognathic growth pattern and anterior rotation of the mandible was seen after GH treatment in GHD and ISS boys and there were no differences in growth response between two groups. The results of this study are somewhat consistent with their results. In this study, the amount of maxillary length in boys in both groups increased more than three SDS and there was no significant difference in the amount of mandibular length in boys between groups during GH treatment (Table 3). However, the mandibular growth increased more in girls with ISS than in those with GHD (Figure 2). As mandibular ramus height, corpus length, and total mandibular length of girls with ISS increased significantly more than that in those with GHD, lower and total anterior facial heights of girls with ISS were overdeveloped in girls with ISS after 2 years after GH treatment.

These results indicated that the interstitial cartilage growth of the condyles by GH is influenced more in girls with ISS than girls with GHD and mandibular growth by GH was in the vertical, not sagittal, direction for girls with ISS. Although there was no significant difference between groups, the ANB was greater in girls with ISS than in other groups. This mandibular vertical growth direction is that included an increase in anterior facial height in girls with ISS appears similar to patients with Turner syndrome. Previous studies reported that total mandibular length increased significantly, thereby increasing anterior facial height in Turner syndrome.[15,16] These catch-up growth patterns would not cause an acromegalic facial profile but a long facial profile, which is not what the patient wants at the start of GH treatment. Therefore, in treatment of girls with ISS and posterior mandibular growth rotation at the start of GH supplementation, GH should be administered carefully and long term follow-up would be necessary.

In this study, posterior cranial base length and maxillary length showed negative and moderate correlation with age (Table 5). Previous studies also reported that the younger the children at the start of GH treatment, the greater the residual growth potential and greater the craniofacial growth promoting effect.[17,18] Anterior cranial base length in boys and mandibular growth in girls could be influenced by GH. These differences in growth area by GH according to sex might be related to sex difference in growth spurts time or residual growth potential.[19] Additionally, increase of mandibular ramus height could be greater in children with ISS than in children with GHD and increase in anterior and posterior cranial base lengths could be greater in children with GHD than in children with ISS. The early cessation of growth in the synchondroses of the cranial base along with the fact that GH affects primary sites with endochondral ossification mean that GH treatment should be started at an early age to improve cranial base development in children with GHD.[19]

This study had several limitations to interpretation of the data: (1) the study included a limited number of subjects, which may limit the ability to extrapolate these findings to the wider population; and (2) although GH treatment could have an effect on craniofacial catch-up growth in short-term, long-term effect should be explored further. Future studies with adequate sample size and long-term follow-up are necessary to evaluate final difference in craniofacial skeletal growth between adults with ISS and those with GHD according to sex.

In summary, craniofacial growth increased toward the norm in children with idiopathic short stature or growth hormone deficiency during growth hormone treatment but some parts of the face may be influenced beyond the normal growth which can lead to an increased mandible and a longer face. In particular, greater increase in mandibular growth and anterior facial height were observed in girls with idiopathic short stature than those in the reference group during growth hormone treatment. Therefore, because growth hormone can result in a long facial profile, due to vertical overgrowth of the mandible, growth hormone treatment should be used with caution when treating girls with idiopathic short stature.

Figure 2 Changes of mandibular growth and anterior facial height by growth hormone (GH) in boys and girls. (A, B, and C) By contrast the results observed in boys, mandibular ramus height, corpus length, and total mandibular length significantly increased more in girls with ISS than in girls with GHD during GH treatment; (D and E) 2 years after GH treatment, lower and total anterior facial heights were significantly greater in girls in the ISS group than in girls in the reference groups. Control = the reference group; GHD = growth hormone deficiency; ISS = idiopathic short stature; T0 = before GH treatment; T1 = at 2 years after start of GH treatment.

Table 4 Mean and standard deviation of cephalometric measurements between groups after growth hormone treatment.

Variables	Boys				Post hoc	Girls				Post hoc
	GHD group[a]	ISS group[b]	Reference group[c]	*p*		GHD group[a]	ISS group[b]	Reference group[c]	*P*	
Linear measurements (mm)										
Anterior cranial base length (N-S)	69.40 ± 2.41	70.2 ± 3.01	69.80 ± 0.98	0.640		67.13 ± 2.47	67.88 ± 1.55	69.00 ± 2.07	0.134	
Posterior cranial base length (S-Ba)	48.55 ± 2.24	50.50 ± 2.59	51.75 ± 2.55	0.144		49.56 ± 1.68	46.38 ± 0.52	44.50 ± 2.93	0.001	a > b, a > c
S-Ba/N-S (%)	69.98 ± 2.97	72.05 ± 4.60	74.12 ± 3.19	0.146		73.87 ± 2.18	68.37 ± 2.35	64.43 ± 2.29	< 0.001	a > b > c
Maxillary length (ANS-PNS)	48.85 ± 2.82	50.00 ± 4.01	48.58 ± 3.57	0.789		49.50 ± 2.12	49.13 ± 1.55	47.56 ± 0.78	0.088	
Mandibular ramus height (Ar-Go)	44.65 ± 3.27	45.85 ± 1.49	46.05 ± 5.75	0.443		42.00 ± 3.95	46.00 ± 4.74	46.00 ± 2.48	0.069	
Mandibular corpus length (Go-Gn)	73.30 ± 6.41	77.65 ± 3.24	77.95 ± 3.76	0.180		75.63 ± 2.13	78.13 ± 2.59	76.88 ± 2.71	0.088	
Ar-Go/Go-Gn (%)	61.26 ± 6.43	59.09 ± 1.73	58.93 ± 4.99	0.849		55.48 ± 4.10	58.78 ± 4.60	59.81 ± 1.52	0.029	
Total mandibular length (Ar-Gn)	103.20 ± 3.21	108.35 ± 5.13	106.80 ± 4.79	0.026		104.88 ± 2.08	109.38 ± 3.62	104.69 ± 4.93	0.052	
Lower anterior facial height (ANS-Me)	70.40 ± 2.87	72.35 ± 3.51	67.31 ± 3.76	0.147		68.31 ± 2.05	71.06 ± 3.36	65.50 ± 3.73	0.026	b > c
Total anterior facial height (N-Me)	123.50 ± 4.90	122.65 ± 7.54	123.06 ± 5.72	0.540		119.00 ± 2.39	128.19 ± 5.95	119.56 ± 6.26	0.007	a < b, b > c
Posterior facial height (S-Go)	78.35 ± 5.90	75.40 ± 2.80	79.70 ± 7.27	0.319		78.50 ± 1.58	78.63 ± 0.52	75.19 ± 3.47	0.007	b > c
Angular measurements (°)										
Cranial base angle (N-S-Ar)	129.40 ± 3.10	127.90 ± 2.22	122.50 ± 1.43	0.260		126.31 ± 4.64	128.25 ± 1.04	129.00 ± 0.93	0.201	
Ramal angle (SN-ArGo)	88.15 ± 2.88	85.65 ± 3.18	87.45 ± 2.72	0.042		87.88 ± 4.35	87.56 ± 1.29	87.25 ± 1.46	0.731	
Gonial angle (Ar-Go-Me)	125.80 ± 3.76	125.35 ± 4.94	124.05 ± 3.15	0.674		126.75 ± 3.12	126.31 ± 1.81	127.00 ± 8.73	0.884	
Mandibular plane angle (SN-GoMe)	33.10 ± 2.23	33.90 ± 3.51	32.00 ± 0.71	0.462		34.25 ± 3.06	35.88 ± 2.59	35.63 ± 9.94	0.373	
Maxilla-cranial base relation (SNA)	79.40 ± 3.06	82.35 ± 1.76	80.58 ± 0.98	0.015	a < b	80.50 ± 2.19	80.81 ± 2.33	78.88 ± 2.79	0.168	
Mandible-cranial base relation (SNB)	76.20 ± 3.26	79.30 ± 1.64	78.81 ± 1.18	0.032	a < b	78.13 ± 2.79	76.88 ± 1.55	75.75 ± 1.67	0.106	
Maxilla-mandible relation (ANB)	3.20 ± 1.55	3.05 ± 1.30	1.77 ± 0.75	0.906		2.38 ± 1.30	3.94 ± 0.78	3.13 ± 2.46	0.122	

P values were calculated by the Kruskal-Wallis test with Bonferroni correction.
GHD = growth hormone-deficient; ISS = idiopathic short stature.

Table 5 Correlation coefficient between sex, age, groups (GHD and ISS), and changes (standard deviation scores) of variables during growth hormone treatment.

Variables	Age		Sex		Groups	
	r	*p*	*r*	*p*	*r*	*p*
Linear measurements (mm)						
Anterior cranial base length (N-S)	0.219	NS	−0.636	***	−0.349	*
Posterior cranial base length (S-Ba)	−0.451	**	−0.157	NS	−0.334	*
Maxillary length (ANS-PNS)	−0.541	***	0.274	NS	−0.008	NS
Mandibular ramus height (Ar-Go)	−0.243	NS	0.246	NS	0.376	*
Mandibular corpus length (Go-Gn)	0.002	NS	0.442	**	0.269	NS
Total mandibular length (Ar-Gn)	−0.353	*	0.446	**	0.207	NS
Lower anterior facial height (ANS-Me)	−0.286	NS	0.182	NS	0.184	NS
Total anterior facial height (N-Me)	0.040	NS	0.156	NS	−0.019	NS
Posterior facial height (S-Go)	−0.195	NS	0.198	NS	−0.161	NS
Angular measurements (°)						
Cranial base angle (N-S-Ar)	0.679	***	−0.038	NS	0.129	NS
Ramal angle (SN-ArGo)	−0.254	NS	0.406	*	−0.014	NS
Gonial angle (Ar-Go-Me)	0.487	**	0.100	NS	0.089	NS
Mandibular plane angle (SN-GoMe)	0.394	*	0.125	NS	0.092	NS
Maxilla-cranial base relation (SNA)	−0.192	NS	−0.337	*	−0.074	NS
Mandible-cranial base relation (SNB)	−0.345	*	−0.312	NS	−0.047	NS
Maxilla-mandible relation (ANB)	0.081	NS	−0.105	NS	0.116	NS

Sex (male, 1; female, 2) and groups GHD = growth hormone-deficient, 1; ISS = idiopathic short stature, 2.
NS = not significant.

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