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The Effect of Growth Hormone Treatment on Craniofacial Growth in Short Stature Children

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Abstract
The purpose of this study is to analyze the effect of growth hormone (GH) treatment on craniofacial growth in growth hormone-deficient (GHD) and idiopathic short stature (ISS). Eleven GHD patients and eleven patients with ISS (with paired sampling who are matching in eleven GHD subjects' age and sex) were two subject group who started to receive GH treatment at the Pediatrics in Yeungnam University Hospital. All subject group were taken lateral cephalogram before, after 2 year GH treatment. As a reference group, we select eleven normal children (NC) with paired sampling who are matching in subjects' age and sex from Department of Orthodontics, Kyungbuk National University Hospital. As a result, the GH treatment generates a positive influence on accelerated growth in several craniofacial components, especially in the posterior total facial height, the cranial base length, and the mandibular length and the increase of mandibular length, cranial base length and posterior facial height. GH treatment over 2 years leads craniofacial catch-up growth, which is pronounced in regions where interstitial cartilage is involved and results in a less convex face in profile.

Keywords: Growth Hormone, Craniofacial Growth, Short Stature Children

Introduction

The stature of children is an important index reflecting genetic influences, health and nutritive conditions. A child is considered to have short stature when he or she is-2SD shorter than the average stature of a child the same age or gender, or if within the shortest three percent.

After birth, craniofacial growth is determined by complex interactions among genes, hormones and nutrients. Since the order, size, proportion and onset age of craniofacial growth are different for each person, growth with age does not occur at the same proportion over the same period[1]. Many studies on craniofacial growth suggest various causes for reducing growth, such as endocrine metabolic and chromosomal diseases, GHD and prenatal causes related to serious craniofacial growth problems, and etc[2-4]. Among these, GH not only influences the growth of stature or craniofacial area, but also internal growth, bone metabolism, muscles and adipocyte tissue[5].

Among researchers studying short stature, Spiegel et al[2]. found that the facial proportion of short-statured children shown by angles is not significantly different from those of same aged NC, though the linear measurement value is relatively smaller. Van Erum et al[6]. said the characteristics of short-statured children (average age 5.1) without GHD were small submaxillary, short basis cranii length, normal anterior facial height and increased lower anterior facial height. By conducting cephalometric radiation analysis on short-statured children (average age one to two), Kjellberg et al[7]. reported that both children with or without GHD are influenced identically in the growth and development of stature and face. The linear measurement values of facial structure were small for most short-statured children with characteristics such as small and flat basis cranii, and mandible relatively located posterior. Although reports have been released on the influence of GH on long-term skeletal growth[5], few studies have been done on the influence of GH on craniofacial structure.

After conducting treatment of relatively high-dosage GH for two years on young girls suffering from Turner's syndrome, Rongen-Westerlaken et al[8]. said the length of the mandible was increased mostly by the vertical growth of the mandibular ramus, and that the mandible used to rotate the posterior started to rotate to the front. Although the maxilla seemed less influenced than the mandible, both the maxilla and mandible showed a tendency of rotation, increasing facial convexity. The length and angle of the anterior/posterior cranial base also showed differences. Injecting GH in children with ISS, Cantu et al[9]. observed catch-up growth occurring in stature, facial height, skeletal age and posterior cranial base. In Korea, Jeong et al[10]. compared between the results of GH treatment for short-statured children and the growth of NC to report that GH treatments show catch-up growth without signs of unbalanced craniofacial growth. Most of these studies are limited in that they do not classify the specific causes of short stature in children due to various causes.

This paper divides short stature caused by GHD and other causes, then compares and analyzes the influence of GH treatment on craniofacial structure.

Material and Methods

Subjects

From 2006, children diagnosed with short stature by the Pediatrics Department of Yeungnam University Hospital were

asked if they would agree to allow measuring their craniofacial structure from a dentist before getting GH treatment. For those who agreed, a lateral cephalometric radiograph was taken under a standard condition of occluding the teeth as much as possible. Fourteen of the subjects were male and eight female. Among them, 11 were in the short-statured group in which the cause was GHD, while the other 11 were in the idiopathic group matched with their GHD counterpart based on age and gender and using data on ISS children.

Children with normal occlusion were selected from elementary schools in Daegu and had Class 1 molar relationships. Using data traced and surveyed for 10 years from May 1983 by the Orthodontics Department of Kyungbuk National University Hospital, 11 children were matched based on age and gender to fit those of the short-statured children. Without an irregular teaching arrangement or asymmetry, the children had good and healthy facial profiles. Therefore, the subjects had an average age of 11, with 21 being male and 12 female (Table 1).

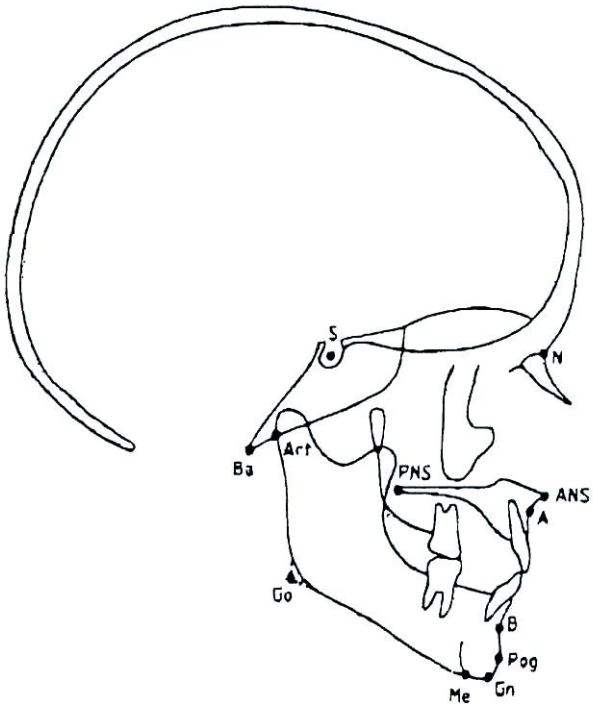
Table. 1. Demographic Characteristics of Subjects

Variables	Groups			Total n=33 (%)
	GHD-SS n=11 (%)	I-SS n=11 (%)	NC n=11 (%)	
Gender				
Male	7 (73.6)	7 (73.6)	7 (73.6)	21 (73.6)
Female	4 (36.4)	4 (36.4)	4 (36.4)	12 (36.4)
Age (M±SD)	11.0±2.0	11.0±2.0	11.7±1.5	11.2±1.8

GHD-SS; Growth Hormone-Deficient Short Stature, I-SS; Idiopathic Short Stature, NC; Normal Children, SD; Standard Deviation

Methods

Lateral cephalometric radiographs of the subject children were taken under the standard condition of occluding the teeth as much as possible. Radiograph was taken twice-once before GH treatment and again after two years of treatment. To confirm the growth of the craniofacial area, 12 caphalometric landmarks were selected (Figure 1). Using these landmarks, 12 linear and seven angular measurements were made (Table 2). The cephalometric measurement was made by one dentist.



1. S (Sella): The center of the sella turcica.
2. Na (Nasion): The most anterior point of the frontonasal suture.
3. A (Subspinale): The most posterior point on the curvature from the anterior nasal spine to the crest of the maxillary alveloar process.
4. B (Supramentale): The most posterior point on the curvature of the mandible between the pogonion and the crest of the mandibular alveloar process.
5. Pog (Pogonion): The most anterior point on the contour of the chin.
6. Gn (Gnathion): A bony point by bisecting the line of angle formed by the facial plane and mandibular plane.
7. Me (Menton): The most inferior point on the symphyseal outline.
8. Go (Gonion): A bony point by bisecting the line of angle formed by the ramal plane and mandibular plane.
9. Ar (Articulare): The point of intersection of the inferior cranial base surface (basioccipital) and the posterior surface of the mandibular condyle.
10. Ba (Basion): The most inferior posterior point on the anterior margin of the foramen magnum.
11. PNS (Posterior nasal spine): The most posteior point on the bony hard palate.
12. ANS (Anterior nasal spine): The most anterior point on the maxilla at the level of the palate.

Figure. 1. Cephalometric Landmarks

Table. 2. Linear and Angular Craniofacial Measurements

Linear	Abbreviation	Cephalometric Land marks	Angular	Abbreviation	Cephalometric Land marks
Anterior cranial base length	ACB	N-S	Saddle angle	SA	N-S-Art
Posterior cranial base length	PCB	S-Ba	Gonial angle	GA	Art-Go-Me
Total cranial base length	TCB	N-Ba	Mandibular plane angle	MPA	S-N-Go-Gn
Upper anterior facial height	UAFH	N-ANS	Position of maxilla	SNA	S-N-A
Upper posterior facial height	UPFH	S-PNS	Position of mandible	SNB	S-N-B
Lower anterior facial height	LAFH	ANS-Me	Maxilla/ Mandible	ANB	A-N-B
Anterior total facial height	ATFH	N-Me	Posterior position of mandible	PPMand	S-N-Art-Go
Posterior total facial height	PTFH	S-Go			
Maxillar length	MaxL	ANS-PNS			
Mandibular ramus length	MandRL	Art-Go			
Mandibular corpus length	MandCL	Go-Pog			
Overall mandibular length	OMandL	Art-Pog			

Statistical Analysis

In the comparison of the craniofacial structures of the two short-statured groups and normal group, an independent sample verification was used. To compare the treatment's effects in the two short-statured groups, repeated two-way ANOVA was used. Also, in order to compare the two groups before and after treatment with the normal group, a one-way ANOVA was used while conducting the bonferroni test for post-verification. The statistical significance level was set at $p<0.05$, and SPSS ver.19.0 was used as a statistical processing program.

Results

Comparing Growth of Linear Craniofacial Structure following GH Treatment

Comparing the Linear measurements, among two short-statured groups before treatment and NC, significant differences were shown in TCB ($p<0.01$), UAFH ($p<0.05$), UPFH ($p<0.05$), PTFH ($p<0.05$), MaxL ($p<0.05$), MandRL ($p<0.05$), MandCL ($p<0.01$), OMandL ($p<0.01$).

In the post-verification, significant differences between two short-statured groups were shown in TCB ($p<0.01$). Between the short-statured children with GHD and NC, significant differences were shown in PCB ($p<0.05$), TCB ($p<0.01$), UAFH ($p<0.05$), UPFH ($p<0.05$), MaxL ($p<0.05$), MandRL ($p<0.01$), MandCL ($p<0.01$) and OMandL ($p<0.05$). Between the ISS children and NC, significant differences were shown in PCB ($p<0.05$), UPFH ($p<0.05$), PTFH ($p<0.05$), MandRL ($p<0.05$) and MandCL ($p<0.05$). For the two groups that received treatments, the effects of treatment were significant for all linear-measurement values ($p<0.01$). No differences, however, were observed in treatment between the two groups. After two years of treatment, values that showed significant differences among the three groups were TCB ($P<0.01$) and MandCL ($p<0.01$). After two years of treatment, the values that showed significant differences between two short-statured groups were TCB ($p<0.01$) and MandCl ($p<0.05$). After two years of treatment, the values that showed significant differences between short-statured children with GHD and NC were TCB ($p<0.01$) and MandCl ($p<0.05$). After two years of treatment, no significant differences were detected between ISS children and NC (Table 3).

Table. 3. Comparison of Mean (±SE) for Linear Craniofacial Variables among 11 GHD-SS Children, 11 I-SS Children Treated with GH and 11 NC

Linear	Mean ± SE (mm) at Start			Mean ± SE (mm) after two years			p^a	p^b	p^c	p^d	p^e	p^f	p^g	p^h	p^i	p^j
	GHD-SS	I-SS	NC	GHD-SS	I-SS	NC										
ACB	65.82 ±0.46	66.46 ±0.85	68.23 ±0.47	68.09 ±2.17	70.00 ±2.72	69.50 ±1.36	.06	.06	.06	.16	.00	.30	.11	-	-	-
PCB	44.32 ±0.86	45.44 ±2.54	48.14 ±3.92	48.68 ±1.91	48.95 ±3.03	49.09 ±3.99	.12	-	.04	.04	.00	.28	.95	-	-	-
TCB	100.59 ±2.81	103.05 ±3.39	104.77 ±3.63	101.91 ±2.88	107.3 ±3.21	107.68 ±3.87	.00	.01	.00	.68	.00	.95	.00	.01	.00	-
UAFH	51.36 ±1.70	52.82 ±4.01	52.55 ±0.72	54.36 ±1.85	55.77 ±3.30	57.41 ±3.61	.04	.88	.04	.40	.00	.93	.07	-	-	-
UPFH	46.59 ±1.63	46.64 ±1.45	49.23 ±3.44	49.45 ±2.12	50.27 ±2.10	51.09 ±3.63	.01	-	.04	.04	.00	.26	.37	-	-	-
LAFH	64.68 ±3.22	65.77 ±4.06	65.03 ±3.80	69.27 ±3.00	71.64 ±3.84	67.51 ±3.73	.78	-	-	-	.00	.29	.05	.38	.75	.20
ATFH	113.50 ±3.14	117.14 ±6.81	118.42 ±6.05	121.18 ±4.42	125.8 ±7.41	123.10 ±6.02	.11	-	-	-	.00	.72	.20	-	-	-
PTFH	69.18 ±3.73	68.18 ±6.18	74.87 ±6.01	79.46 ±4.61	77.00 ±3.41	80.50 ±6.24	.01	-	.05	.02	.00	.35	.24	-	-	-
MaxL	43.50 ±2.35	45.95 ±4.54	47.41 ±3.37	48.36 ±2.40	50.14 ±3.72	49.39 ±3.77	.04	.34	.04	-	.00	.52	.47	-	-	-
MandRL	37.45 ±3.70	39.09 ±4.74	43.36 ±5.09	44.95 ±4.28	45.55 ±3.36	46.95 ±5.56	.01	-	.01	.04	.00	.37	.56	-	-	-
MandCL	69.05 ±4.25	71.14 ±2.72	74.91 ±4.07	73.64 ±4.84	77.91 ±3.01	78.59 ±3.46	.00	.18	.00	.04	.00	.33	.01	.04	.01	-
OMandL	96.59 ±4.13	100.14 ±4.92	103.05 ±5.86	103.00 ±2.56	106.2 ±4.96	107.46 ±4.64	.01	.06	.01	05	.00	.69	.06	.05	.05	.98

SE; Standard Error, GHD-SS; Growth Hormone-Deficient Short Stature, I-SS; Idiopathic Short Stature, NC; Normal Children, a; p value of two-way ANOVA among groups at start, b; p vale of bonferroni test between GHD-SS and I-SS at start, c; p vale of bonferroni test between GHD-SS and NC at start, d; p vale of bonferroni test between SS-I and NC at start, e; p value of main effects between treatment period and group in repeated two-way ANOVA, f; p value of interaction effects between treatment period and group in repeated two-way ANOVA, g; p value of one way ANOVA among groups after two years, h; p value of bonferroni test between GHD-SS and I-SS after two years, i; p value of bonferroni test between GHD-SS and NC after two years, j; p vale of bonferroni test between I-SS and NC after two years.

Comparing Growth of Angular Craniofacial Structure following GH Treatment

Comparing the angular measurements among short-statured children with GHD before treatment, ISS children before treatment and NC, no significant differences were found. The same went for the post-verification as well. After two years of treatment, no significant differences were detected among the three groups in angular measurements. The two groups that received treatments showed significant effects in SA ($p<0.01$), MPA ($p<0.01$), SNB ($p<0.01$) and ANB ($p<0.01$), but none from treatment between the two groups (Table 4).

Table. 4. Comparison of Mean (±SE) for Angular Craniofacial Variables among 11 GHD-SS Children, 11 I-SS Children Treated with GH, and 11 NC

Angular	Mean ± SE (mm) at start			Mean ± SE (mm) after two years			p^a	p^b	p^c	p^d	p^e	p^f	p^g	p^h	p^i	p^j
	GHD-SS	I-SS	NC	GHD-SS	I-SS	NC										
SA	126.32 ±5.43	126.32 ±3.64	123.73 ±3.09	127.36 ±4.77	128.32 ±1.95	124.09 ±3.94	.25	-	-	-	.01	.39	.05	-	.14	.05
GA	127.91 ±3.93	125.50 ±1.34	124.32 ±5.18	125.68 ±3.23	126.05 ±4.31	123.41 ±5.82	.09	-	-	-	.32	.11	.35	-	-	-
MPA	35.91 ±3.67	36.14 ±2.88	32.91 ±5.45	33.91 ±3.36	34.00 ±3.03	31.64 ±6.36	.14	-	-	-	.00	.82	.39	-	-	-
SNA	79.41 ±2.93	80.59 ±2.83	80.32 ±2.92	79.59 ±2.94	81.27 ±2.28	81.03 ±3.22	.61	-	-	-	.34	.57	.33	-	-	-
SNB	75.86 ±4.24	76.32 ±2.83	77.59 ±2.43	77.14 ±3.49	78.09 ±2.02	78.69 ±2.87	.44	-	-	-	.00	.55	.44	-	-	-
ANB	3.55 ±1.60	4.27 ±1.21	2.68 ±1.49	2.45 ±1.37	3.18 ±1.37	2.34 ±1.61	.05	.74	.51	.05	.00	-	.34	-	-	-
PPMand	88.64 ±4.71	87.36 ±2.03	87.36 ±2.03	89.46 ±3.65	86.82 ±2.83	87.32 ±2.85	.56	-	-	-	.80	.22	.12	-	-	-

SE; Standard Error, GHD-SS; Growth Hormone-Deficient Short Stature, I-SS; Idiopathic Short Stature, NC; Normal Children, a; p value of two-way ANOVA among groups at start, b; p vale of bonferroni test between GHD-SS and I-SS at start, c; p vale of bonferroni test between GHD-SS and NC at start, d; p vale of bonferroni test between I-SS and NC at start, e; p value of main effects between treatment period and group in repeated two-way ANOVA, f; p value of interaction effects between treatment period and group in repeated two-way ANOVA, g; p value of one way ANOVA among groups after two years, h; p vale of bonferroni test between GHD-SS and I-SS after two years, i; p vale of bonferroni test between GHD-SS and NC after two years, j; p vale of bonferroni test between I-SS and NC after two years.

Discussion

Prior studies on effect of GH treatment on craniofacial growth in short stature children have limits of not classifying the specific causes for children suffering from short stature.

Therefore, this study divided short-statured children into those with GHD and those who were ISS to examine their growth aspects and observe the influence of growth catalyst (GH treatment) on growth.

When comparing the craniofacial structures of two short-statured groups, the TCB value was significantly low for short-statured children with GHD. Other than that, no significant differences were discovered but when comparing short-statured children with GHD and NC, significant differences were shown in PCB, TCB, UAFH, UPFH, MaxL, MandRL, MandCL and OMandL. This data is consistent with the results of previous research except for MaxL. When comparing ISS children and NC, significant differences appeared in PCB, UPFH, PTFH, MandRL and MandCL. The result suggests that influence is characteristically shown solely on the posterior cranial base, posterior facial height and mandible. The characteristics described above are connected with one another, and the phenomena is caused by a failure in the growth of mandible and posterior cranial base.

Comparing the craniofacial structures of two short-statured groups, differences were only recognized in cranial bases. Nonetheless, when the two short-statured groups were compared with the normal group, the differences were greater in short-statured children with GHD because the craniofacial structures of short-statured children with GHD are smaller. In 1986, Takano et al[11]. studied the growth condition of craniofacial structures of patients with GHD and ordinary children with small stature, and found no significant differences between the two groups. The measurements for the craniofacial structures of the two groups were found to be small not because of GHD, but rather of small physical characteristics.

The two-year GH treatment, which took place in this study, had growth promotion effects on both groups, and no significant difference in the effects of treatment was seen between the two groups. The major factor behind growth is the increase of length in the skeletal system. The vertical increase of bones is caused by enchondral ossification, and bone growth occurs when cartilaginous tissue changes to osseous tissue. Generally, bone length is increased during chondrification or enchondral ossification, while bone circumference expands during periosteal ossification[12].

After two years of treatment, differences between the two groups were shown in TCB and MandCL, suggesting that the growth of the cranial base and mandible for short-statured children with GHD was insufficient compared to that for ISS children. On the effect of GH on the cranial base, treatment after age 7 is known to be unable to bring the values up to normal range since ACB is integrated around age 7, and growth after that point is made by bone infiltration at nasion. The result of this study showed that ISS children are no different from NC after two years of treatment, suggesting that catch-up growth occurred in all measurements. On the other hand, short-statured children with GHD had differences with NC in TCB and MandCL even after two years of treatment, suggesting that although catch-up growth happened in the cranial base and mandible, it failed to reach normal levels. Ranly[13]. said synchondrosis closed by ossification cannot be reacted again by injecting GH which indicates that GH treatments for short-statured children should start before the spheno-occipital synchondrosis closes to ensure more growth promotion effects.

The limit of this study was that the size of the subjects was too small-scale to show differences based on age and gender, making the results difficult to generalize. In the future, more subjects are needed to observe the long-term effects of GH treatments on the craniofacial complex, specifically for each age group, gender, factor and period.

In conclusion, Delayed growth and failed catch-up growth for short-statured children influence not only height but also the growth of craniofacial area. In addition, GH treatments are

safe and effective treatments for spurring growth in short-statured children. The treatments were shown to effect general craniofacial catch-up growth, which was most clearly seen in areas related to in-between cartilaginous growth.

Conclusions

Short-statured children generally have small and degenerative faces due to their short and flat cranial base and small mandible located posterior. As a result, delayed growth and failure of catch-up growth for short-statured children are related not only to height but also to growth of the craniofacial area. In addition, GH treatments are safe and effective for normalizing the growth of short-statured children. They resulted in general craniofacial catch-up growth, which was most clearly seen in areas related to in-between cartilaginous growth. No significant differences, however, were found between two short-statured groups.

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