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Changes on craniofacial structures in children with growth-hormone-deficiency

RESUMEN

Objetivo: describir el crecimiento diferencial de las estructuras craneofaciales en niños con deficiencia de hormona de crecimiento tratados con reemplazo hormonal.

Métodos: estudio transversal de 46 pacientes (*n* = 14 niñas, 32 niños) entre cuatro y 18 años de edad, categorizados en dos grupos pareados: 23 individuos sanos y 23 pacientes con deficiencia de hormona de crecimiento bajo terapia de reemplazo. Las diferencias fueron evaluadas con *t* de Student para muestras independientes.

Resultados: se obtuvieron mediciones pequeñas para todas las estructuras faciales con diferencias significativas en la longitud total de la mandíbula (Co-Pg, $p > 0.03$), altura facial anteroinferior (ANS-Me, $p > 0.03$) y altura facial total (N-Me, $p > 0.02$), además de un tipo facial retrógnata. En las niñas, la longitud de la base craneal posterior fue más corta (S-Ba 29.14 ± 3.02 mm) y se observó un ángulo mandibular plano elevado (40 ± 5.50º), amplia relación anterior maxilomandibular (5.86 ± 1.57º), con diferencias significativas ($p < 0.05$ y $p < 0.04$) comparadas con el grupo de referencia.

Conclusiones: debe considerarse la morfología cefalométrica de referencia en la población al comenzar la terapia con hormona de crecimiento.

SUMMARY

Objective: to describe the growth of craniofacial structures in growth-hormone deficiency (GHD) children during growth-hormone therapy (GHT).

Methods: a cross-sectional sample of 46 subjects (*n* = 14 girls, 32 boys) aged 4-18 years was obtained. They were categorized into two paired groups: the reference group, for comparing the cephalograms, consisted in 23 healthy subjects, and the study group (23 patients) with GHD under GHT. Differences between groups were assessed by independent t-tests.

Results: the boys showed smaller measurements for all facial structures presenting significant differences in total mandibular length (Co-Pg $p < 0.03$), lower anterior facial height (ANS-Me $p < 0.03$) and total anterior facial height (N-Me $p < 0.02$) as well as retrognathic facial type. In girls the posterior cranial base length was shortened (S-Ba 29.14 ± 3.02 mm) and show a high mandibular plane angle (40 ± 5.50º) a wide relation anterior maxillo-mandibular (5.86 ± 1.57º) with a statistical difference ($p < 0.05$ and $p < 0.04$) compared with the reference group.

Conclusions: we suggest considering the cephalometric morphology at the beginning of GHT.

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Key words
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Introduction

Growth is a dynamic process that begins at conception.[1] Control of postnatal craniofacial skeletal growth involves complex interactions of genes, hormones and nutrients. Linear somatic growth and maturation are influenced and controlled by various hormones, particularly growth hormone (GH), which is secreted by the pituitary.[2] Hyposecretion of GH during development leads to dwarfism. Hypersecretion of this hormone from pituitary adenomas prior to closure of the growth plates during adolescence results in gigantism, whereas during adulthood it results in acromegaly.[3] Growth hormone deficiency (GHD) is a disease that leads to growth disturbances, including short stature, acromicria and distinctive craniofacial features as a result of inhibited pituitary gland hormones.[4] In the GHD, the length and depth of the face are inappropriately small for the child's age, with the face maintaining childlike convexity.[5]

Many studies have reported mandibular total length (Co-Pog) is reduced, primarily as a result of the small ramus height. In addition, the maxilla is significantly reduced, and there may be a comparable degree of reduction in the mandible. The maxilla is often retrognathic but is affected less than the mandible.[6-9] Concerning cranial base size, many studies have reported that the posterior cranial base length is smaller than the anterior cranial base (S-N) length.[10]

Growth hormone therapy implies a direct impact of GH on bone mass and bone size. In the craniofacial complex, this hormone regulates cartilage formation. GH treatment accelerates craniofacial growth in children, and face height is altered by GH, particularly by influencing the height of the posterior face. GH has also been proposed to affect the rotation of the mandible during craniofacial growth.[11,12] In our community no have reports on the effects of the GH therapy in craniofacial structures. Therefore, this project aimed to describe the differential growth of craniofacial structures in children with GHD, during treatment with replacement therapy.

Methods

The study was conducted in Tampico City, Tamaulipas, Mexico, and the ethics and research committee of the General Regional Hospital. *Instituto Mexicano del Seguro Social,* approved the study. Subjects with congenital or chromosomal anomalies and children treated with orthodontic functional applian-ces were excluded from the study. Data was obtained from a cross-sectional sample of 46 patients (n = 14 girls, 32 boys) aged 4-18 years previous informed consents obtained from their parents before to participate in the study. The subjects were categorized into two paired groups: the reference group, for comparing the cephalograms, consisted in 23 healthy subjects from a elementary school and a high school selected by sampling no probabilistic, and the study group conformed for 23 patients with GHD under replacement therapy at the endo-crinology pediatric service. The criteria used to diagnosed GHD in patient were consisted in two standard deviations or more below the normal mean height for subjects of a similar age and gender, GH level below 10 ng/mL after stimulation with L-DOPA, arginine or clonidine and low insulin-like growth factor 1 (IGF-1). The patients were injected daily 0.03 mg/kg/day 6 to 7 times a week for a mean of 3.74 ± 2.98 years.

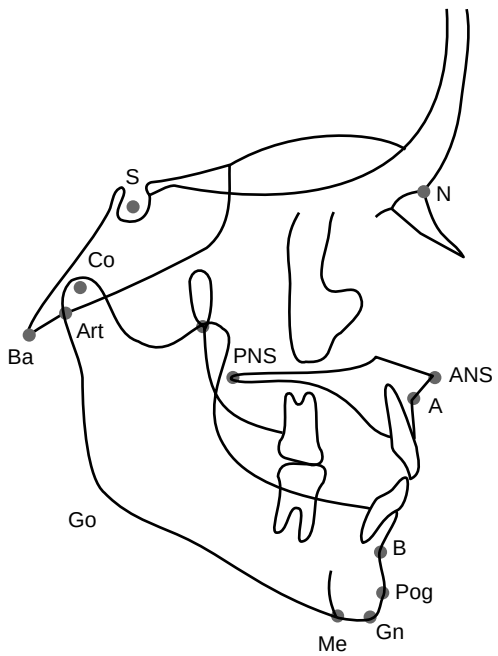

Figure 1. Cephalometric landmarks of the lateral cephalogram. A = point A, ANS = anterior nasal spine, Art = articulare, B = point B, Ba = basion, Co = condylion, Gn = gnathion, Go = gonion, Me = menton, N = nasion, PNS = posterior nasal spine, Pog = pogonion, S = sella turcica

All measurements were conducted on schools premises in the morning and in the department of pediatric endocrinology in the afternoon. Participants removed their shoes and wearing light clothing. Body weight was measured recorded to the nearest 0.1 kg using a digital scale (Tanita Corporation, Japan). Height was obtained by using a portable stadiometer 225 cm (SECA, Hamburg, Germany) to nearest 0.1 cm. BMI was calculated as weight (kg) divided by height squared (m^2). Body composition was assessed by BIA using a TANITA TBF310 model with a frequency of 50 kHz. Height, sex and age were entered manually, while weight was recorded automatically using 0.5 kg as an adjustment for clothing weight in all subjects.

Standard lateral cephalometric, panoramic and hand-wrist radiographs were taken for each subject. The radiographs were taken under standardized conditions, with the teeth in maximum intercuspation for the head images. All cephalometric radiographs were traced and 12 landmarks were identified (figure 1). The cephalograms were measured twice by two independent observers with a one month interval. No significant ($p > 0.05$) inter or intra observer error was found. Dental age was assessed from panoramic radiographs via the method established by Demirjian et al.[13] Bone age was determined by analyzing the left hand-wrist radiographs using standards of Gruelich and Pyle.[14]

Descriptive statics were used by groups and sex; values are expressed as means ± SD. Differences

between the study group and reference group were assessed by independent t-tests. A p-value less than 0.05 were regarded as significant.

Results

On average, the reference and treated group in both sexes did not differ significantly in bone age and dental age but in general, the reference group had a higher weight and was both taller.

We compare the mean values of all linear measurements for individuals with GHD and the standard values for individuals of the same sex and chronological age group. Among boys showed smaller measurements for all facial structures presenting significant differences in total mandibular length (Co-Pog $p < 0.03$), lower anterior facial height (ANS-Me $p < 0.03$) and total anterior facial height (N-Me $p < 0.02$) as well as retrognathic facial type compared with the reference group. The mean for the upper jaw length (ANS-PNS) is 55.19 ± 4.27 mm, presents a minimal deficit in the position in relation to the cranial base (S-N-A 80.25 ± 3.10º) and retropositioned mandible (S-N-B 76.13 ± 2.98º). The angular measurements showed a slight increment in mandibular plane angle (S-N/Go-Gn 34.63 ± 5.08º), and wide cranial base angle (N-S-Art 127.31 ± 7.44º). Among girls also presented smaller measurements except anterior upper face height (N-ANS 50.86 ±

Table I
Somatic and craniofacial measurement of the studied population*

	Boys			Girls		
	Healthy	**GHD**	***p***	**Healthy**	**GHD**	***p***
Chronological age	12.74 ± 2.87	12.74 ± 2.87	—	10.71 ± 3.14	10.71 ± 3.14	—
Bone age	12.06 ± 3.08	11.59 ± 3.81	0.70	10.29 ± 2.43	9.43 ± 3.4	0.59
Dental age	13.58 ± 2.86	12.57 ± 3.10	0.34	11.35 ± 3.06	11.5 ± 2.7	0.92
Height (m)	1.58 ± 0.16	1.43 ± 0.15	0.01**	1.46 ± 0.18	1.25 ± 0.11	0.02**
Weight(kg)	50.24 ± 14.26	38.66 ± 13.31	0.02**	39 ± 11.95	26.97 ± 10.47	0.06
BMI (kg/m2)	19.63 ± 2.22	17.88 ± 2.93	0.06	17.81 ± 1.74	17.35 ± 4.36	0.80
Linear variables						
S-N (mm)	71.38 ± 4.6	68.56 ± 3.93	0.07	64.86 ± 2.73	63.86 ± 3.71	0.57
S-Ba (mm)	34.5 ± 3.05	32.8 ± 3.41	0.15	32.14 ± 3.48	29.14 ± 3.02	0.11
ANS-PNS (mm)	54.69 ± 5.22	55.19 ± 4.27	0.76	51 ± 2.76	52 ± 3.65	0.57
Art-Go (mm)	46.19 ± 5.6	45.06 ± 7.24	0.62	40.29 ± 2.62	38.86 ± 3.71	0.42
Go-Pog (mm)	73.81 ± 5.71	70.81 ± 7.36	0.20	67.86 ± 5.39	67.71 ± 7.93	0.96
Co-Pog (mm)	115.19 ± 7.5	108.56 ± 8.95	0.03**	105.86 ± 6.6	101.57 ± 11.6	0.41
N-ANS (mm)	55.19 ± 4.05	52.69 ± 3.84	0.08	50.43 ± 3.3	50.86 ± 4.25	0.83
N-Me (mm)	120.56 ± 7.34	114.25 ± 7.93	0.02**	110.57 ± 5.96	108.57 ± 10.4	0.66
S-Go (mm)	78.13 ± 9	73.12 ± 7.69	0.10	68.57 ± 4.68	64.43 ± 5.74	0.16
ANS-Me (mm)	69.38 ± 4.64	60.25	0.03**	62.71 ± 2.87	60.43 ± 5.76	0.36
Angular variables						
S-N-A (º)	82.25 ± 4.21	80.25 ± 3.1	0.13	81.14 ± 2.47	80.14 ± 3.43	0.55
S-N-B (º)	77.44 ± 4.01	76.13 ± 2.98	0.30	76.43 ± 2.5	74.14 ± 3.89	0.21
N-S-Art (º)	126.31 ± 5.53	127.31 ± 7.44	0.66	126.57 ± 3.25	128.43 ± 7.41	0.55
A-N-B (º)	4.63 ± 1.89	4.31 ± 2.21	0.67	4.14 ± 1.21	5.86 ± 1.57	0.04**
S-N/GoGn (º)	34.06 ± 6.09	34.63 ± 5.08	0.77	34.86 ± 3.02	40 ± 5.5	0.05**

**All values are mean ± SD*

*** Statically significant.*

S-N = anterior cranial base length, S-Ba = posterior cranial base length, ANS-PNS = upper jaw length, Art-Go = ramus length, Go-Pog = mandibular corpus, Co-Pog = total mandibular length, N-ANS = upper anterior face height, N-Me = total anterior face length, S-Go = total posterior face height, ANS-Me = lower anterior face height, S-N-A = cranial base, S-N-B = position of the mandible, N-S-Art = cranial base angle, A-N-B = relation anterior maxillomandibular, S-N/GoGn = mandibular plane angle

4.25 mm) and upper jaw length (ANS-PNS 52 ± 3.65 mm). The posterior cranial base length was shortened (S-Ba 29.14 ± 3.02 mm). For the angular measurements showed a high mandibular plane angle (40 ± 5.50º) a wide relation anterior maxillomandibular (5.86 ± 1.57º) with a significant difference (S-N/GoGn $p < 0.05$ and A-N-B $p < 0.04$) compared with the reference group and wide cranial base angle (N-S-Art 128.43 ± 7.41º) (table I).

The GHD therapy group differed from the controls particularly in their decreased distance from sella turcica to posterior nasal spine (S-PNS), short mandibular corpus (Go-Pog) and moderate deficits from mandibular ramus height (Ar-Go) and total mandibular length (Co-Pog). Both maxillary length (ANS-PNS) and cranial base angle (N-S-Art) were increased in both sexes but in girls the A-N-B is wide. The proportions between anterior and posterior face heights and between lower and slightly upper anterior face heights were also smaller than those of the reference group.

Discussion

Growth hormone is essential for normal growth during childhood and adolescence and influences bone mineralization and body composition in children. Patients with growth hormone deficiency display significant maturational delays and reduced somatic growth. In this study the subjects with GH therapy presents stills delays in height and weight. The bone age and dental age not present delays significant. As previously reported,[15] dental delay was significantly less than the delay in skeletal age. Further, there was no significant growth hormone treatment effect on dental maturation as showed in other studies.[16] The lack of a therapeutic response would indicate that dental age is less influenced and less sensitive to growth hormone than somatic and craniofacial growth.

A few studies have examined the effects of GH therapy on craniofacial growth in children with GHD and have shown a tendency for catch-up growth. Anterior facial heights and mandibular ramus lengths were the most retarded before treatment and demonstrated the greatest catch-up growth. This resulted in a more normal facial appearance and correction of the mandibular retrusion.[17] We found that the craniofacial measurements were short in patients with GH therapy, especially the mandible and the cranial base. The ramus height, mandibular corpus and total mandibular length failed to display any significant growth. The possible explanation for this is that the mandible is the least affected of the individual measurements with GH therapy and also by growth and development cephalometric features reported in Mexican children. This studies reported mandibular retrusion in relation to the cranial base, mandibular open angle, short mandibular body and biprotusion alveolar.[18-23] Our results additionally showed an increment in measures of antero-posterior maxilla length, mandibular plane angle and A-N-B angle, the improved growth in maxillary length might be explained by a stimulative effect of GH in the cartilaginous nasal septum and by the typical predisposing craniofacial morphology in Mexican children.

This study is the first to describe the craniofacial features in patients with GH therapy and presents some limitations such that when using cross-sectional samples, the craniofacial morphology in patients untreated with GH and the degree of GHD are unknown. The synchondroses in the cranial base complete earlier, causes differential growth of the craniofacial skeleton. 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. Therefore is important begin the GH therapy as early as possible. We must consider the cephalometric morphology reference reported in Mexican children and the collaboration of the orthodontist to evaluate the craniofacial measures at begins the therapy and the end of treatment. We need to continue with a longitudinal study to examine the effects of GH in younger age on craniofacial growth in patients with GHD.

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