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Craniofacial morphology aspects in children with isolated growth hormone deficiency – a cephalometric study

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Abstract

Craniofacial and dental morphology is influenced by different circulating hormones, but it is of particular importance that there is growth hormone (GH) in normal craniofacial and teeth development. Craniofacial morphometry studies in children with GH deficiency show different changes in certain anthropometric variables in the sense of reducing their values compared to normal children's developmental norms in different stages of childhood and adolescence. Therefore, the early establishment of GH replacement therapy can correct craniofacial morphological changes induced by GH deficiency. In our study, we evaluated different anthropometric craniofacial variables at children with GH deficiency and we established some anthropometric and morphological characteristics associated with this pathology.

Keywords: growth hormone, lateral cephalogram, cephalometric points, anthropometric analyzes.

Introduction

The most important role of growth hormone (GH) is the longitudinal bone growth through primary action on growth cartilage [1–10]. GH also interferes in bone remodeling, mineralization and osteoblast hypertrophy [11]. GH deficiency may also affect craniofacial growth, but also tooth formation and eruption [12]. There are many causes that cause craniofacial growth disorders: chronic diseases, metabolic diseases (diabetes), endocrine diseases, chromosomal causes [13–16].

GH deficiency may be from pituitary etiology but may involve different clinical forms – combined pituitary deficiency and isolated GH deficiency (IGHD). IGHD is associated with three forms, two transmitted autosomal recessives (type IA and IB) and a form transmitted dominant autosomal (type II). Also is described bioinactive GH syndrome as a cause of stature hypotrophy [17, 18].

Modifications in craniofacial growth in the sense of the reduction of this increase occur in children with idiopathic small stature, IGHD, low gestational age and genetic diseases (Turner syndrome, dwarfism, Russell–Silver syndrome) [19]. There are studies on the craniofacial characteristics of children with these pathologies, studies that take into account different anthropometric variables, thus establishing different craniofacial typologies [19–23]. All of these studies are limited by the reduced number of subjects, but their results reveal craniofacial growth changes characteristic to different etiologies. In general, the GH deficiency leads to an aspect of immature face being modified both the longitudinal and the horizontal dimensions.

Aim

In our study, we evaluated different anthropometric craniofacial variables at children with GH deficiency, and we established some anthropometric and morphological characteristics associated with this pathology.

Participants, Materials and Methods

The study was performed on 13 cases (nine boys and four girls). The subjects included in the study had age between nine to 13 years old, known for IGHD having recombinant GH treatment. We had the informed consent of the legal representatives of the patients included in the study for data use. GH values were lower than 10 ng/mL in challenge tests, waist standard deviation (SD) less than 2 SD (according to auxological parameters). A lateral cephalometric radiography was performed on all subjects, in accordance with standardized rules, and we are identified the cephalometric points (Figure 1). The cephalometric variables taken in the study were: n–s (nasion–sella) or anterior cranial base; s–ba (sella–basion) or posterior cranial base; n–ba (nasion–basion) or total cranial base; ss–ba (subspinale–basion) or maxillary prognathism linear measure; sp–gn (the most anterior point of maxilla–gnation) or lower face height; s–pm (sella–pterigo maxilar fissure) or upper posterior face height; pm–ba (posterior point of maxilla–basion)

or maxillary prognathism linear measure; pm–ss (posterior point of maxila–subspinale) or maxillary length; gn–go (gnathion–gonion) or mandibular length; SNA angle (sella nasion to A point angle – A point is the most concave point of anterior maxilla, similar to subspinale point); SNB angle (sella nasion to B point angle – B point is the most concave point on mandibular symphysis, similar to supramentale point); ANB angle (A point to B point angle); ML–NL angle (angle of maxillo-mandibular relations – ML is mandibular line, NL is nasal line); s–n–sm angle (mandibular prognathism angle); s–n–ss angle (maxillary prognathism angle).

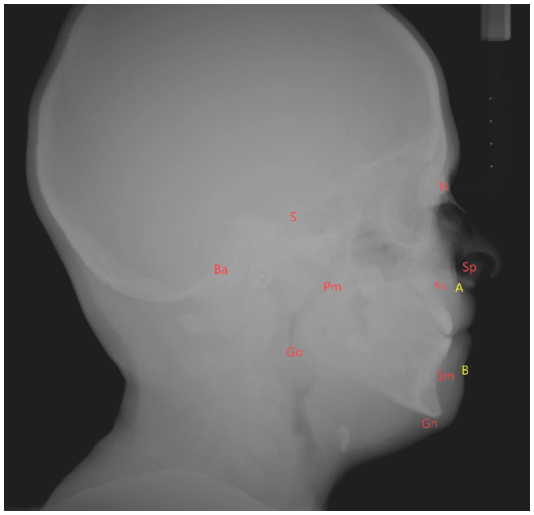

Figure 1 – ***Cephalometric points on the lateral cephalogram: 13-year-old, male patient with IGHD. IGHD: Isolated growth hormone deficiency.***

Cephalometric analyzes were performed manually by a single investigator.

The values of the parameters measured on the cephalometry were processed with the Microsoft Excel program (Microsoft Corp., Redmond, WA, USA), along with the XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and the IBM *Statistical Package for the Social Sciences* (SPSS) Statistics 20.0 program (IBM Corporation, Armonk, NY, USA).

The evaluated parameters of the subjects included in the study were stored in type files Excel.

Secondary data processing, calculation of fundamental statistical parameters, average and the SD of their ratio – the coefficient of variation and their graphical representation was made with Excel, using the Pivot Tables, Functions–Statistical commands, Chart and the Data Analysis module. To perform data normality tests (Shapiro–Wilks and Anderson–Darling) and Student's *t*-test and Analysis of Variance (ANOVA) test, XLSTAT module commands were used.

Results

The linear measurements, expressed in mm, refer to the length of the base of the cranium (anterior cranial base n–s, posterior cranial base s–ba and total cranial base n–ba) and the length of the mandible (gn–go), given the fact that these cephalometric variables are affected by the IGHD. Another linear measurement we made that refer on maxillary length (ss–pm), lower face height (sp–gn), upper face height (n–sp), posterior face height (s–pm).

The results of the cephalometric measurements are listed in Table 1.

Table 1 – ***Mean values and standard deviation (SD) for cephalometric measurements***

Variables	Mean	SD
n–s [mm]	61.91	2.46
s–ba [mm]	35.57	5.82
n–ba [mm]	86.83	6.28
ss–ba [mm]	77.17	4.36
sp–gn [mm]	53.9	6.27
n–sp [mm]	45.83	4.18
pm–sp [mm]	39.64	2.53
s–pm [mm]	43.3	3.95
pm–ba [mm]	39.4	5.34
pm–ss [mm]	37.26	3.63
gn–go [mm]	61.17	5.17
SNA angle [°]	75.96	3.77
SNB angle [°]	76.24	4.84
ANB angle [°]	3.85	2.65
ML–NL angle [°]	26.5	8.29
s–n–ss angle [°]	78.73	2.38
s–n–sm angle [°]	75.54	4.37

The mean values we obtained will be further analyzed and discussed in comparison with other studies, in the following section of our study.

The measured angles refer to the mandible's and maxilla's retrognathism. According to Steiner's analysis, normal standard values can be found for the SNA°, SNB° and ANB° angles: SNA° 82±2°, SNB° 80±2°, ANB° 2±2°.

A decrease of the SNA^0, SNB^0 angles' value can be noticed compared to the normal values. However, the mean value for ANB° surpasses the standard value in our group. Another way of appreciating the mandibulo-maxillary relations can be done from the perspective of angles s–n–ss° and s–n–sm°.

The prognathism angles of the maxilla (s–n–ss) and mandible (s–n–sm) have low values compared to the control group. Thus, there is a difference of about 4 mm between the mean value of the angle s–n–sm in our group and the value of this angle in the control group, in order to reduce this angle in subjects with IGHD (Table 2).

Table 2 – ***Comparing our obtained results with the values of the normal subjects (after Dumancic et al. [23] study)***

Group	Our study group		Reference		Student's *t*-test
Variable	*Mean*	*SD*	*Mean*	*SD*	*p-value*
n–s [mm]	61.91	2.46	63.74	3.09	0.047
s–ba [mm]	35.57	5.82	39.67	2.18	<0.001
n–ba [mm]	86.83	6.28	94.35	4.04	<0.001
n–sp [mm]	45.83	4.18	47.87	3.14	0.044
pm–sp [mm]	39.64	2.53	48.2	2.64	<0.001
sp–gn [mm]	53.9	6.27	57.88	4.62	0.008
gn–go [mm]	61.17	5.17	65.24	4.3	0.003
ML–NL angle [°]	26.5	8.29	21.32	4.78	0.002
SNA angle [°]	75.96	3.77	82		<0.001
SNB angle [°]	76.24	4.84	80		<0.001
ANB angle [°]	3.85	2.65	2		<0.001

Group	Our study group		Reference		Student's *t*-test
Variable	*Mean*	*SD*	*Mean*	*SD*	*p-value*
s–n–sm angle [°]	75.54	4.37	79.37	3.67	<0.001
s–n–ss angle [°]	78.73	2.38	80.94	3.65	<0.001

SD: Standard deviation.

The ML–NL angle, which also indicates the maxilla's and mandible's retrognathism, does not have standardized values. Nonetheless, we will discuss these values in the following section by comparison to other studies.

We calculated the correlation coefficients between different cephalometric variables and the correlations between the age and the cephalometric variables, the values of these coefficients being listed in Tables 3 and 4.

Table 3 – ***Coefficients of correlation between cephalometric variables***

	s–ba	n–ba	n–s	gn–go
ss–ba	0.216	0.681	0.477	0.211
s–n–sm	-0.052	-0.744	-0.713	0.1

Table 4 – ***Correlation between age and cephalometric variables***

	n–s	s–ba	n–ba	pm–ba	ss–ba	pm–sp	pm–ss	s–n–ss	s–n–sm	gn–go
Age	0.394	0.652	0.657	0.527	0.6	-0.153	0.002	0.017	-0.195	0.878

Regarding correlations between age and cephalometric variables, we observed high positive ones between age and total cranial base (s–ba), posterior cranial base (n–ba), maxillary prognathism linear measure (pm–ba) and anterior cranial base (s–n) and high negative correlations between age and mandibular length (gn–go).

The correlation coefficients between the prognathism angle of the mandible and the anterior skull base show a negative value, which means a highly significant negative correlation (-0.713), meaning that the reduction of the prognathism angle of the mandible is accompanied by the increase of the dimensions of the anterior skull base. Age is positively highly correlated with the length of the mandible, the correlation coefficient having the value of 0.878. Significant correlations exist between age and total skull base and between age and posterior skull base, which means that as you grow older, the skull base also grows.

The prognathism angle of the maxilla (s–n–ss) and mandible (s–n–sm) does not correlate with age.

For the analysis of the results obtained by us, we used as normal values the data obtained in the Dumancic *et al.* study [23] (Table 2).

Discussions

Considering that the investigation method uses X-ray, for comparison with the control group, we used the data from the literature. We did not collect cephalometric data with subjects without pathology and therefore we have referred to the reference studies, which contain data similar to our study, regarding the age of the subjects and the pathologies of the same etiologies.

From the calculated mean values, we noted that both the maxillary prognathism angle and the mandibular prognathism angle have low values compared to normal values (SNA° 82±2°, SNB° 80±2°). Taking into account that the subjects under study have a treatment period with GHs up to 12–24 months, we can refer to the Funatsu *et al.* study, which reveals SNB° values comparable to our values with an average of 76.24°. Regarding SNA°, we find lower values in our study, with an average of 75.96°, compared with the Funatsu *et al.* study, which indicates an average of 79.2°. However, the values of the prognathism angles of the maxilla and the mandible show a specific reduction in GH deficiency of various etiologies [21, 22]. Another observation of ours is that the two average angles are numerically equal, but they fit the subjects into the retrognathism changes of the mandible and maxilla. Another variable measured by us is ss–ba, which indicates the distance between the basion and the maxilla's concave and the mean values in our group show a significant reduction to the mean control values reported by Dumancic *et al.* (84.01 mm) and even lower values than the group of subjects with Turner syndrome [23], this variable demonstrating once again the retrograde of the maxilla.

The mandibular and maxillary retrognathism is demonstrated by SNA° and SNB°, which in turn are influenced by the abnormal position of the nasion and the height of the face. Even if the nasion does not have a fixed position in the growth and development period, an anterior position of this point may reduce the ANB° and a posterior position of the nasion will increase the ANB° value according to Steiner's analysis, this angle actually expresses the relationship between the maxilla and the mandible. In our group, the average ANB° value is 3.85°, which demonstrates a posterior position of the nasion point. Also, ANB° increase also explains the posterior rotation of the mandible and the maxilla. The mandibular and maxillary retrognathism specific to children with IGHD, but is also found in the morphological picture of Turner syndrome [23]. Apart from the SNB° calculation, the posterior skull base is another anthropometric variable indicating the mandibular retrogression. In our study, the value of the posterior skull base is reduced compared to the normal values.

The prognathism angles of the maxilla (s–n–ss) and mandible (s–n–sm) presents lower values in our group, compared to the control group, but the low value is specific for GH deficiency [23].

The ML–NL angle indicating the rearward mandibular recession of the mandible shows increased values in our study (26.5°), the normal values in the control groups being 21.32° in average.

The anterior cranial base (n–s) is another anthropometric variable recognized as being reduced at children with growth deficiency. In our study, we have a value of 61.9 mm, and there are notable differences between our study and the Funatsu *et al.* study reporting 63.9 mm for girls and 64.9 mm for boys [21]. We find a significant reduction in the anterior cranial base at children in our study.

Regarding the relationship between the anterior cranial base and the posterior cranial base, the values obtained by us reveal a much lower posterior cranial base compared to the previous one (35.57 mm *versus* 61.91 mm), aspect reported in other studies [24, 25].

The height of the anterior face in the lower segment (sp–gn) shows an average value of 53.9 mm, slightly reduced compared to other studies [21, 23], and comparatively reduced to normal subjects.

Total face height (n–sp + sp–gn) has an average value of 99.73 mm, this anthropometric variable being slightly reduced relative to the mean values of the control groups [23], which demonstrates a slightly reduced overall height.

The length of the mandible (gn–go) is reduced compared to the reference groups from our study, with an average of 61.17 mm, but this variable is also in the profile of children with GH deficiency [19–21]. The length of the maxilla is reduced compared to the reference groups (39.64 mm *versus* 48.2 mm).

The morphological modifications of the skull typically to children with IGHD fall largely in the results of other studies, noting that our study is limited by the reduced number of patients. We find out from our results that the previous skull base is reduced [21, 26], while another study [25] reports a normal skull base value.

The value of the correlation coefficient of 0.681 between maxillary prognathism linear measure (ss–ba) and total cranial base (n–ba) shows the prediction value of ss–ba for n–ba (total length of the skull base), which means that there is a correlation between the maxillary retrognathism and the total skull base, in the conditions in which there is a reduction on ss–ba distance compared to the normal reference values. Thus, the retrognathism maxilla is in relation to the total skull base.

There is a positive and significant correlation between maxillary prognathism linear measure (ss–ba) and anterior cranial base (n–s), thus explaining the correlation between the retrognathism of the maxilla and the anterior skull base.

Between the prognathism angle of the maxilla (s–n–sm) and the posterior cranial base, there is a highly significant inverse correlation with a value of -0.744 for the correlation coefficient. The same aspect was found for the correlation between the angle of prognathism of the maxilla and the posterior cranial base.

In our study, correlations between the skull base and age demonstrate a highly significant correlation coefficient (0.657) between the total cranial base (n–ba) and age. Note also that there is a significant correlation between posterior cranial base (s–ba) and the age, the correlation coefficient of 0.652. Compared to the Dumancic *et al.* study [23], we observe higher values of correlation coefficients at control groups, with the statement that our study is limited by the reduced number of subjects.

The prognathism angle of the maxilla (s–n–ss) does not correlate with age; this note is also found in the Dumancic *et al.* study [23].

From the linear variables of the maxilla, we find significant correlation coefficients between pm–ba and age (0.527) and between ss–ba and age (0.6), these values not being within the normal range of the reference group from the Dumancic *et al.* study [23]. The other variables measured in the maxilla do not show correlations with age.

The mandibular prognathism angle (s–n–sm) does not show correlations with age.

The length of the mandible (gn–go) shows a high correlation with age, the value of the correlation coefficient being 0.878.

From the analysis of correlation coefficients between different anthropometric variables and age, we can state that the high prediction value has the posterior cranial base, maxillary prognathism linear measure (pm–ba, ss–ba) and mandible length (gn–go).

The craniofacial morphological characteristics of the group studied by us show a reduction of the posterior base of the skull, the reduction of the mandible and the maxilla, the mandibular and the maxilla retrognathism. Even if our group has a small number of subjects, our values are within the craniofacial typology characteristic to children with GH deficiency.

It should also take into account that dentition and its development are an important part of craniofacial development. It is known that dentition maturation has a moderate delay on children with stature hypotrophy of various causes [27–31]. At patients with asthma hypotrophy, occlusal defects were compared with malocclusions encountered on the normal population [32]. Last but not least, the proper and healthy functioning of one's body is an important aspect of a complete life, the basis for the overall health and the factor that influences the most the human behavior. An impaired functioning causes difficulties in carrying out daily activities, which may at some point lead to mental health problems, such as anxiety or depression [33].

Knowing these abnormalities and changes is important for the orthodontist specialist to apply the correct and appropriate treatment. GH administration leads to accelerated craniofacial development, which improves occlusion and facial profile [21, 34–40]. There are studies that compared some anthropometric variables before and after the treatment with GH and most of them show an improvement on the facial profile without facial disharmony [21]. However, GH therapy cannot greatly influence craniofacial growth, but can correlate with the appropriate times of orthodontic treatment.

There is a limitation in the interpretation of our data in the sense that the number of subjects studied is small, but we must take into account the frequency of this pathology in the general population, which is about 1/3480–1/10 000 live births [41].

Conclusions

Craniofacial characteristics at children with IGHD show a reduction in linear cephalometric variables and calculated angles, which are related to the cranial base, mandible and maxilla length, face length and mandibular and maxillary retrognathism. These changes have as result an immature face aspect, less in relation to age and conserving the child-like convexity. Our cephalometric study shows us the presence of aberrant craniofacial

aspects, with reduction of the posterior cranial base, shortening of the maxilla and mandible, retrusion of the maxilla and mandible. The retrognathism of the mandible and maxilla is best evidenced by the values of the SNA° and SNB°, easy to calculate on the lateral cephalogram. The posterior cranial base directly influences the maxillary–mandibular skeletal relationships and therefore it is necessary to calculate this cephalometric variable, also easy to highlight on the lateral cephalogram. Recognition of these three cephalometric variables, the cranial base, mandible and maxilla length and mandibular and maxillary retrognathism, and their calculation is the starting point in orthodontic therapy in patients with IGHD.

Conflict of interests

None to declare.

Authors' contribution

Smaranda Adelina Preda and Dana-Maria Albulescu equally contributed to this article.

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