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A cephalometric study on craniofacial morphology of Iranian children with beta-thalassemia major

Structured abstract

Authors – Amini F, Jafari A, Eslamian L, Sharifzadeh S **Objective** – To study cephalometric and facial features of Iranian children with beta-thalassemia major.

Design – Lateral cephalometric radiographs of thalassemic patients and controls who were matched for age, sex and ethnic origin were analyzed and compared. **Setting and Sample Population** – A total of 30 thalassemic patients (18 male and 12 females) from Aliasghar Hospital, and 30 controls from the Orthodontic Department of Azad University.

Outcome measure – Size and shape differences in the craniofacial complex between thalassemic patients and controls.

Results – All thalassemic patients had a Class II skeletal base relationship with an average ANB angle of 8.75°. There was no record of dramatic maxillary prognathism. However, the mandible of the thalassemic patients appeared to be smaller in size and more retruded in the face. A pronounced vertical growth direction was evident from angular and linear measurements. The dental deviations in thalassemic patients were mainly seen in the proclination and significant overeruption of incisors and increased overjet. Marked convex lower face and prominent upper and lower lips were evident from soft-tissue measurements. **Conclusion** – Anemia does not only produce overgrowth of the maxilla. It also produces a retardation of condylar and ramal growth of the mandible producing Class II skeletal pattern.

Key words: anemia; cephalometry; craniofacial growth; thalassemia major

Introduction

Thalassemias are the commonest monogenic diseases worldwide. Thalassemia is found in some 60 countries with the highest prevalence in the Mediterranean region, parts of North and West Africa, the Middle East, the Indian subcontinent, southern Far East and southeastern Asia; together they compose the so-called 'thalassemia belt' (1–6). In western countries, thalassemia affects mostly those whose bloodlines are traceable to high prevalence areas (4–6). About 150 million people worldwide carry beta-thalassemia genes. The genes are particularly prevalent in Sardinia (11–34%) and Sicily (10%) both provinces of Italy (7,8). Other regions with a high gene frequency are Greece (5–15%), Turkey and Iran with 4–10% (9–11). Iran, like many other countries in the region, has a large number of beta-thalassemia patients. The gene frequency of alpha-thalassemia is very rare in Iran, but beta-thalassemia is high and varies considerably from area to area, having its highest rate of more than 10% around the Caspian Sea, and Persian Gulf (9–13).

One of the systemic manifestations of thalassemia, which is of esthetic concern, is bone marrow expansion (overgrowth) especially of the skull (Fig. 1). The prominent characteristics of such patients are facial dysmorphology and malocclusion (13–17). Caffey and Baker described the appearance of these thalassemic patients as 'rodent face' (18,19). Dentofacial manifestations of beta-thalassemia reported in the literature are a Class II malocclusion, a protrusive premaxilla with flaring and spacing of the upper anterior teeth, increased overjet and reduced overbite, prominent malar bone, depres-



Fig. 1. Patient with facial deformities secondary to beta-thalassemia.

sion of the bridge of the nose and partially obliterated maxillary sinus (13–22). Almost all of these features are of orthodontic concern and therefore it is important to understand the changes associated with thalassemia and their implications for orthodontic treatment.

Quantitative assessments of the skeletal morphology of patients with thalassemia major are rare (15,16). It is distressing to learn that, one of the commonest monogenic diseases worldwide has attracted so little, almost nil attention. Therefore, the purpose of this investigation was to identify the cephalometric and facial features of Iranian children with beta-thalassemia major.

Materials and methods

The patients were selected as per their enrollment with the Ali Asghar hospital, which is the biggest treatment centre for these patients in Iran. During a period of 6 months, out of 173 patients reported to the hospital, 36 children suffering form thalassemia had made lateral cephalograms for the purpose of orthodontic treatment, out of which six lateral cephalograms were rejected due to poor image quality. Therefore, lateral cephalograms of 30 children (18 male and 12 female) with thalassemia major with a mean chronological age of 10.4 ± 4.29 year were available for this study. All patients were in a stable condition and no patient had received any orthodontic treatment.

Each thalassemic patient was matched with a normal control on the basis of chronological age $(\pm 6 \text{ months})$ and sex. The mean chronological age of the control group, which was selected from the pre-treatment the orthodontic records of department, was 10.01 ± 3.25 year. The control group had no history of orthodontic treatment, and did not present with craniofacial syndromes. Both the sample and the control group were of the same ethnic origin. All 60 lateral cephalograms were taken under standardized conditions with the teeth in occlusion and lips in relaxed position. Forty-two linear and angular cephalometric parameters defining craniofacial morphology (22 skeletal, 13 dentoalveolar, and 7 soft-tissue) were selected (Figs 2-6). For bilateral landmarks the midpoint between the right and left images was used. Any discrepancies in landmark position were resolved by mutual agreement between the authors. Angular and



Fig. 2. (A) Lateral cephalogram of a 11.9-year-old boy with a severe form of beta-thalassemia. (B) Tracing of the cephalogram.



linear measurements were recorded to the nearest 0.5° and 0.5 mm, respectively. The 9.2 percent magnification of the radiographs was not corrected, as all radiographs were taken on the same machine.

Fourteen cephalograms were randomly selected, traced, measured, and verified by a second observer and the reliability of 28 random parameters was examined by means of inter-group correlation. The method error was assessed using Dahlberg's formula (23). Descriptive statistics, including the mean, standard deviation (SD) and difference between means for each group were computed. The cephalometric data of thalassemic patients and controls were compared by means of a Mann–Whitney test for independent samples.

Results

Measurement error

Fig. 3. Skeletal angular measurements: 1, SNA (Sella-Nasion-point A); 2, SNB (Sella-Nasion-point B); 3, ANB; 4, NSAr (Nasion-Sella-Articulare); 5, SArGo (Sella-Articulare-Gonion); 6, NGoAr (Nasion-Gonion-Articulare); 7, NGoMe (Nasion-Gonion-Menton); 8, ArGoMe (Articulare-Gonion-Menton); 9, SN/GoGn (SN line-mandibular plane); 10, SN/ANS-PNS (SN line-palatal plane); 11, ANS-PNS/MP (basal plane angle).

The correlation coefficients ranged from 70 to 95 percent and all were statistically significant ($p \le 0.01$). The error of the method (Dahlberg's formula) did not exceed 0.77° or 0.56 mm.





Fig. 4. Skeletal linear measurements: 12, S-N (distance between points Sella and Nasion); 13, S-Ar (distance between points Sella and Articulare); 14, Ar-Go (distance between points Articulare and Gonion); 15, Go-Me (distance between points Gonion and Menton); 16, S-Go(distance between points Sella and Gonion); 17, N-Me (distance between points Nasion and Menton); 18, N-ANS (distance between points Nasion and Anterior Nasal Spine); 19, ANS-Me (distance between point Anterior Nasal Spine); 19, ANS-Me (distance between Anterior Nasal Spine); 20, ANS-PNS (distance between Anterior and Posterior Nasal Spines); 21, SE (distance between Sella and Articulare points projected perpendicularly onto S-N line); 22. SL (distance between Sella and Pogonion point projected perpendicularly onto sella-nasion line).

Body growth

Comparing body length of both groups, the thalassemic patients were 89.5% (129.8 ± 11.3 cm) of the control group (145.0 ± 10.8 cm). The main differences between craniofacial features of thalassemic patients and the controls are shown in Table 1.

Horizontal skeletal pattern

In general, measurements of the cranial base did not significantly differ from the control group. Similarly, insignificant differences between thalassemic patients and controls did not indicate any enlargement of the maxillary base in the horizontal plane (SNA = 79.8° and ANS-PNS = 51.6 mm). However, statistically significant differences were found in relation to the

Fig. 5. Sagittal and vertical dentoalveolar measurements: 23, I-NA (angle between upper Incisor long axis-NA line); 24, I-SN (upper Incisor long axis-Sella-Nasion plane angle); 25, I-NB (angle between lower Incisor long axis-NB line); 26, I-GoMe (lower Incisor long axismandibular plane angle); 27. I/I (angle between the long axis of upper and lower incisors); 28, UM \perp ANS-PNS (perpendicular distance from the mesio-buccal cusp of the second deciduous or Upper first permanent Molar to the nasal line); 29, UI \perp ANS-PNS (perpendicular distance from the incisal point of maxillary incisor to the nasal line); 30, LM \perp GoMe (perpendicular distance of the mesio-buccal cusp of the Lower second deciduous or first permanent Molar to the mandibular plane); 31, LI \perp GoMe (perpendicular distance of the incisal point of Lower Incisor to the mandibular plane); 32, I-NA (distance between the incisal edge of maxillary incisor and Nasion-A line); 33, I-NB (distance between the incisal edge of mandibular incisor and Nasion-B line); 34, Overjet (sagittal distance between the incisal edges of maxillary and mandibular incisors); 35, Overbite (vertical distance between the incisal edges of maxillary and mandibular incisors).

mandible (SNB, Go-Me, N-Go-Me, Ar-Go-Me, and SL). The mandible of the patients appeared to be smaller in size (Go-Me = 59.04 mm and SL = 35.75 mm) and more retruded in the face (SNB = 71.22°). Relative to the control group, there was a statistically significant class II skeletal pattern (ANB 8.57° vs. 3.58°) ($p \le 0.001$) among thalassemic patients.

Vertical skeletal pattern

The increase in lower anterior facial height (LAFH), articulare (S-Ar-Go), mandibular and maxillo-mandibular



Fig. 6. Sagittal and vertical soft-tissue measurements: 36, gl-sn-pg (angle between glabella, subnasale and the soft-tissue pogonion points); 37, sn-ls/li-pg (angle between a line passing through subnasale and labrale superius points, and a line passing through labrale inferius and the soft-tissue pogonion points); 38, NLA (angle between a line passing through subnasale and tangential to the inferior contour of nose, and a line passing through subnasale and tangential to labrale superius); 39, ANS-PNS/ls-con (angle between nasal line and the contour line of labrale superius passing through the soft-tissue A point and the superior point of labrale superius); 40, ANS-PNS/li-con (angle between nasal line and the contour line of labrale inferius passing through the soft-tissue B point and the inferior point of labrale inferius); 41, sn-pg \perp ls (perpendicular distance of labrale superius point to a line passing through subnasale and the soft-tissue pogonion points); 42, sn-pg \perp li (perpendicular distance of labrale inferius point to a line passing through subnasale and the soft-tissue pogonion points).

(ANS-PNS/Go-Gn) angles in the thalassemic group were highly significant ($p \le 0.001$) indicative of a severe vertical growth pattern. Another contribution to this growth pattern was reduced posterior face height (S-Go = 66.35 mm vs. 71.05 mm), which was also statistically significant ($p \le 0.02$). Anti-clock wise rotation (1.4°) of palatal plane was statistically insignificant. Reduced vertical height of the ramus of mandible was also less significant ($p \le 0.05$).

Dentition

The overjet was significantly increased in this sample (6.3 mm) and the interincisal angle was reduced by 13.9°, which was statistically highly significant. The maxillary and mandibular incisors were proclined recorded from linear measurements (I-NA and I-NB) but their inclinations (I-NA° and I-SN° for upper and I-NB° for lower incisors) were within the normal range. However, the mandibular incisor position to mandibular plane (I-GoMe°) was recorded as proclined. Except for upper molars (UM \perp ANS-PNS), both upper and lower incisors (UI \perp ANS-PNS and LI \perp GoMe) as well as lower molars (LM \perp GoMe) had extruded significantly.

Soft tissue features

Cephalometrically, the thalassemic patients were found to exhibit a more convex profile than the control group (gl-sn-pg). Marked convex lower face (sn-ls-pg) and prominent upper (ANS-PNS/ls-con and sn-pg/ls) and lower (ANS-PNS/li-con and sn-pg/li) lips were evident from all the measurements.

Discussion

Though, Iran's national thalassemia screening program has been largely successful and has resulted in a 70% reduction in the expected annual birth rate of affected infants, still the continuing battle against genetic diseases is a constant challenge (9,24). There are no previous reports on the craniofacial characteristics of Iranian children suffering from thalassemia.

Matching with a control group for this study posed a special problem as it had been previously reported that there was a tendency for growth retardation in patients with thalassemia major (2,18,25). Bassimitci et al. (15) argued that matching of thalassemic patients with normal subjects on the basis of skeletal age is not a reliable method, but they suggested no alternatives. Considering that chronological age is bound to result in a relative reduction in the thalassemic patient's linear

Table 1. Differences between thalassemic patients and control subjects

Parameters	Thalassemia (n = 30), mean ± SD	Control (n = 30), mean ± SD	Difference between mean values	Level of significance
S-N (mm)	67.95 ± 1.58	67 00 + 3 76	0.04	
$S-\Lambda r$ (mm)	07.93 ± 1.30	07.99 ± 5.70	1.71	
	100 10 + 2 00	104.26 ± 2.45	0.19	
Maxilla	122.10 ± 3.02	124.30 ± 3.43	2.10	
	70 70 + 2 92	90 12 1 2 49	0.24	
ANG DNG (mm)	19.10 ± 2.02	50.12 ± 2.40	1 19	
And-FNG (mm)	51.05 ± 5.05	50.45 ± 4.00	-1.10	
	71.00 . 0.00	76 46 + 2 45	E 04	***
$SIND(^{-})$	71.22 ± 3.02	76.40 ± 3.43	5.24	***
	59.04 ± 4.18	65.17 ± 7.23	0.13	
NGOAT (2)	33.07 ± 3.11	34.00 ± 4.12	-1.01	***
	80.57 ± 5.54	74.28 ± 5.58	-6.29	***
	135.03 ± 5.03	129.35 ± 5.00	-6.08	*
Ar-Go (mm)	39.33 ± 3.88	41.98 ± 6.02	2.65	
SE (mm)	17.52 ± 3.07	18.05 ± 3.45	1.13	**
SL (mm)	35.75 ± 7.73	44.00 ± 10.73	8.25	
Maxilio-mandibular	0.57 0.70		4.70	1. 1. 1.
ANB (°)	8.57 ± 2.79	3.85 ± 1.90	-4.72	***
Vertical skeletal				
N-Me (mm)	114.39 ± 5.66	112.45 ± 9.67	-1.94	
N-ANS (mm)	46.88 ± 3.29	49.99 ± 5.12	3.11	**
ANS-Me (mm)	71.72 ± 6.23	64.88 ± 6.22	-6.84	***
S-Go (mm)	66.35 ± 5.38	71.05 ± 9.34	4.70	*
SArGo (°)	145.50 ± 4.75	141.62 ± 5.83	-3.88	***
SN/GoGn (°)	42.27 ± 6.77	33.06 ± 6.03	-9.21	***
SN/ANS-PNS (°)	7.64 ± 2.17	9.05 ± 3.79	1.41	
ANS-PNS/MP (°)	37.39 ± 5.51	26.74 ± 6.00	-10.65	***
Dental horizontal				
I-NA (°)	15.43 ± 4.68	15.35 ± 6.33	-0.08	
I-SN (°)	94.21 ± 5.76	94.99 ± 8.00	0.78	
I-NA (mm)	6.32 ± 2.83	3.38 ± 2.22	-2.94	*
I-NB (°)	21.83 ± 4.60	23.78 ± 6.12	1.95	
I-GoMe (°)	95.75 ± 4.79	90.21 ± 8.36	-5.54	**
I-NB (mm)	2.32 ± 1.30	4.63 ± 1.89	2.31	*
Dental vertical				
UM \perp ANS.PNS (mm)	21.62 ± 2.62	21.23 ± 3.99	-0.39	
UI ⊥ ANS.PNS (mm)	31.73 ± 3.41	26.03 ± 4.39	-5.70	***
LM ⊥ GoMe (mm)	30.75 ± 2.16	27.96 ± 3.55	-2.79	**
LI ⊥ GoMe (mm)	42.40 ± 4.17	38.64 ± 4.92	-3.76	***
Interdental				
Overjet (mm)	6.32 ± 2.38	3.00 ± 1.36	-3.32	**
Overbite (mm)	2.32 ± 1.30	2.37 ± 1.56	0.05	
/ (°)	123.76 ± 5.93	137.70 ± 9.80	13.94	***

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Parameters	Thalassemia (n = 30), mean ± SD	Control (n = 30), mean ± SD	Difference between mean values	Level of significance
gl-sn-pg (°)	159.30 ± 5.88	164.68 ± 5.39	5.38	***
sn-ls-pg (°)	133.86 ± 9.72	156.25 ± 11.66	22.39	***
NLA' (°)	105.62 ± 14.34	105.93 ± 10.47	0.31	
ANS.PNS/Is-con (°)	144.48 ± 7.25	104.95 ± 10.03	-39.53	***
ANS.PNS/li-con (°)	31.09 ± 7.61	38.21 ± 10.05	7.12	**
sn-pg-ls (mm)	7.93 ± 1.94	4.65 ± 1.78	-3.28	***
sn-pg-li (mm)	7.07 ± 1.85	4.01 ± 2.00	-3.06	***
Height				
Height (cm)	129.80 ± 11.30	145.00 ± 10.80	15.20	***

Table 1. Continued

SD, standard deviation.

* $p \le 0.05$; ** $p \le 0.01$; *** $p \le 0.001$.

measurements and appreciating the 89.5% reduction in the height of thalassemic patients in this study, the results were analyzed. The retarding effect of thalassemia on general skeletal growth has been reported earlier (2,18,25). If premature fusion of the epiphysis of the long bones in thalassemic patients leads to shortening of the proximal humerus (13) then deformities of the cranial base could be anticipated considering the similarities between the synchondrosis of the cranial base and the epiphysis of the long bones. However, this was not reflected in the cranial base measurements. Similar findings were reported in the study of Bassimitci et al. (15). Alhaija et al., however, revealed that thalassemic patients have significantly reduced craniofacial dimensions, apparently as part of total growth retardation (16).

Prominent craniofacial manifestation of orthodontic concern among thalassemic patients included a Class II skeletal relationship associated with a strong vertical growth pattern. Similar findings were also reported in the studies of Bassimitci et al. (15), Alhaija et al. (16) and case reports of Drew and Sachs (13). The large intermaxillary discrepancy (ANB) could be attributed to a smaller mandible and further complicated by a short ramus. Other measurements such as SE and SL also indicated a short mandible (Fig. 4, parameter 21 & 22). The values representing the maxilla, on the other hand, pointed toward a normal maxilla in the sagittal plane (Table 1). This is in accordance with the findings of Bassimitci et al. (15) and Alhaija et al. (16). Our findings, however, are not in line with others, who have reported that because of more cancellous bone-containing marrow spaces in maxilla there is a dramatic maxillary prognathism (18–21,26–29). Probably, these case reports lacked a control group and therefore led the authors to find the fault with the maxilla. The development of a Class II pattern could also be attributed to the fact that the mandible grows slower than the maxilla and therefore is being blocked by the excessive vertical maxillary growth (13). Bassimitci et al. considered the reduction in saddle angle and shortening of the posterior cranial base as factors that might lead to maxillary prognathism (15). However, the role of the cranial base, in the development of Class II malocclusion was ruled out in this study as the values were within the normal range.

A pronounced vertical growth direction of the mandible in these patients seemed to be a consistent finding in almost all publications (15,16). Various explanations for this pronounced vertical growth direction have been reported such as muscular weakness (1), mouth breathing pattern (30), vertical decent of the posterior maxilla (due to enlargement of the maxillary marrow spaces) (15) and probably a deficient ramus and condylar growth. This can be explained in the view of the fact that the subperiosteal growth of the ramus as well as the secondary cartilage of the mandible are equally sensitive to various causes of growth retardations like severe chronic anemia (18), endocrine dysfunction (31,32) and growth hormone insensitivity (33), an issue that deserves more study.

Mean overjet value was increased for thalassemic patients in this study. This was not in agreement with that of Bassimitci et al. (15). The dentoalveolar compensation in the vertical plane (average overbite) was seen in the form of overeruption of the upper and lower incisors similar to previously published studies (15,16).

In agreement with results of the previous study (15), the facial appearance of thalassemic patients followed their substantial skeletal discrepancy. The smaller chin was accompanied by a tendency to more prominent lips (reduced interlabial angle). Interestingly, Abu Alhaija (34) in another investigation reported that the thalassemic patients had a smaller tongue size, shorter soft palate, smaller upper, and middle pharyngeal length. Whether these alterations of the uvulo-glossopharyngeal dimensions are direct cause of skeletal alterations is unknown.

Among the limitations of the present study, it has to be mentioned that the patients in this study represent a small sample of Iranian thalassemic patients, and therefore, further investigations performed on larger groups of patients are recommended. Longitudinal studies are also needed to determine the pattern and amount of growth from childhood into adulthood. With recent technologies such as stereophotogrammetry, laser scanning, range cameras, optoelectronic instruments and electromagnetic digitizers, the limitations of the lateral cephalograms used in this study can be overcome in the future investigations (35). These technologies provide a threedimensional, non-invasive, detailed analysis of the facial characteristics of the patient and can be performed frequently without any additional biological burden on the patients.

Conclusions

Children with thalassemia major, irrespective of the ethnic background, exhibited a distinct craniofacial morphology characterized by a Class II skeletal pattern with a strong vertical component. The literature records only the skeletal overgrowth of the maxilla and zygoma. However, from the results of the present study it can be concluded that as a result of anemia, retardation of growth especially of the condyles and the ramus of the mandible leads to the development of facial dysmorphology.

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