Original Article

A radiographic study on craniofacial morphology and dental development in the Jordanian patients with ß-thalassemia major

ABSTRACT

Objective of the Study: This study aimed to study the cephalometric features of Jordanian patients diagnosed with ß-thalassemia major and compare their dental development with their chronological age.

Subjects and Methods: This was a case–control study. Lateral cephalometric radiographs of 27 thalassemia patients and controls (matched for age and ethnic origin) were analyzed and compared. Panoramic radiographs of 18 thalassemia patients were analyzed by the Demirjian system to assess their dental development and compare with their chronological age using *t*-test, with $P < 0.05$ set as the level of statistical significance.

Results: Thalassemia patients exhibited a highly significant difference, compared to the controls, in sagittal relationship (ANB), mandibular plane inclination (MxP/MnP), anterior rotation of the maxilla (SN/Mxp), the ratio of posterior to anterior face height, and the upper incisors' distance to the maxillary base ($P < 0.005$). Prominent upper and lower lips ($P < 0.001$) and an acute nasolabial angle ($P < 0.05$) were evident in thalassemia patients compared to controls. Thalassemia patients had a delay in dental development with advancing age. Furthermore, there was a statistically significant correlation ($P < 0.001$) between the extent of this delay and chronological age, which indicates that the delay increases, as the patient gets older.

Conclusions: Jordanian ß-thalassemia major patients have a Class II skeletal pattern, a prominent vertical growth direction of the mandible, protruded upper and lower lips, and proclined upper incisors. Furthermore, they have a delay in dental development with advancing age.

Keywords: Cephalometric, dental development, growth retardation, ß-thalassemia major

INTRODUCTION

Thalassemia is an inherited disorder of hemoglobin (Hb) synthesis. ß-thalassemia major is one of the severe forms of the disease, which is widespread throughout many countries in the world, particularly in the Mediterranean region and Southeast Asia.[1] In Jordan, according to the National register, there are 1011 patients diagnosed with thalassemia major in all its variants.

Dentofacial manifestations are reported in the literature as common manifestations of ß-thalassemia major. These manifestations include a Class II malocclusion, a protrusive premaxilla with flaring and spacing of the upper anterior teeth, increased overjet, reduced overbite, and prominent malar bones [Figure 1].[2,3] Almost all of these features are of orthodontic concern, and therefore, it is important to

Juman Mohammad Al-zaben, Dima Hamdi Bader[1], Razan Jamil Salaymeh[2]

Orthodontic Department, [1]Oral Medicine Department, [2]Pediatric dental Department, Al-Bashir Hospital, Amman, Jordan

Address for correspondence: Dr. Juman Mohammad Al-zaben, Department of Dental, Orthodontic Clinic, Al-Bashir Hospital, P. O. Box: Amman, Jordan.
E-mail: jumanmohdalzaben@gmail.com

Received: 25-Mar-2019 **Revised:** 23-Jun-2019
Accepted: 25-Jun-2019 **Published:** 23-Sep-2019

Access this article online	
Website: www.orthodrehab.org	Quick Response Code
DOI: 10.4103/ijor.ijor_13_19	

How to cite this article: Al-zaben JM, Bader DH, Salaymeh RJ. A radiographic study on craniofacial morphology and dental development in the Jordanian patients with ß-thalassemia major. Int J Orthod Rehabil 2019;10:105-11.

understand the changes associated with thalassemia and their implications for orthodontic treatment.

The first comprehensive orthodontic cephalometric study was undertaken in Turkey,[4] followed by Jordan,[5] Iran,[6] and Malaysia.[7] These studies showed that thalassemia patients have typical cephalometric features of a Class II skeletal pattern, a normal position of the maxilla in the sagittal plane, shorter mandibular dimensions, and vertical growth direction together with prominent upper and lower lips [Figure 2]. In addition, it has been reported that there is a retardation of skeletal maturation and dental development in thalassemia children when they reach pubertal growth. This was explained due to hormonal disturbances, low Hb-ferritin level, and suboptimal chelation therapy.[8-11]

The aim of this study is to compare dental age (DA) and skeletal, dentoalveolar, and soft-tissue variables between Jordanian patients with ß-thalassemia major and a control group of the same ethnicity, matched with chronological age.

SUBJECTS AND METHODS

A case–control study was conducted at the orthodontic and pediatric dental clinic in Al-Bashir Hospital-Amman/Jordanian Ministry of Health. Ethical approval for the study was obtained from the Research Committee of the Ministry of Health on 21/5/2014, and informed consent was obtained from the parents of all participants. The thalassemia and control patients were referred from the thalassemia center in Al-Bashir Hospital. This governmental hospital is the largest hospital in the country, and the thalassemia center provides comprehensive medical treatment to approximately 750 thalassemia patients of different nationalities. Thalassemia patients are usually referred to the orthodontic clinic for esthetic reasons and to the pediatric dental clinic for treatment of dental caries and discoloration.

Twenty-seven thalassemia patients (18 males and 9 females, aged 6–21 years) agreed to participate in the study. The inclusion criteria were patients who were diagnosed to have ß-thalassemia major. Patients with current or previous orthodontic treatment or possess any other acquired or congenital craniofacial deformity were excluded from the study. Each thalassemia patient was matched with normal control on the basis of chronological age (±12 months). The control group had no history of orthodontic treatment and did not present with craniofacial deformities. Both the sample and the control groups were of the same ethnic (Jordanian) origin.

First, all 27 thalassemia patients were measured by height and weight, according to the standard growth charts of the center of disease control (CDC).

Second, all 55 (27 thalassemia and 28 controls) individuals had lateral cephalograms taken under the standardized conditions with the teeth in occlusion and lips in a relaxed position. The machine is Carestream Dental: CS 8100SC, magnification panoramic: 1.2 (±10%), and cephalometric: 1.13 (±10%).

Twenty-nine linear and angular cephalometric parameters defining craniofacial morphology (22 skeletal, 4 dentoalveolar, and 3 soft tissue) were selected [Table 1]. The cephalometric points and planes were analyzed by a conventional cephalometric assessment [Figure 3]. Wylie's analysis was added to detect if any maxillary or mandibular prognathism is present in the thalassemia group. This is used purely as an assessment of anteroposterior dysplasia, where it shows

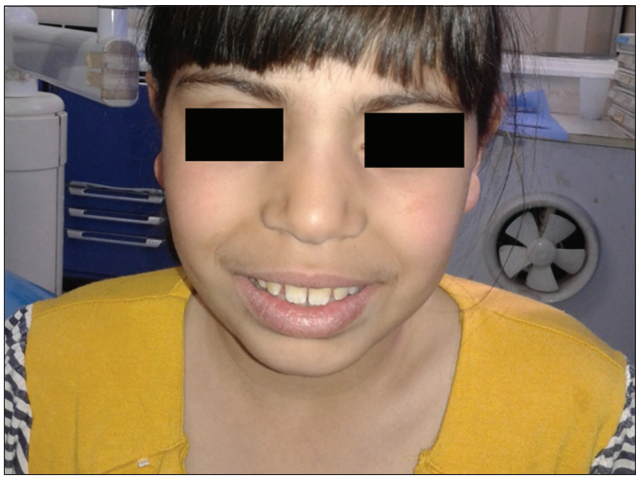

Figure 1: Dentofacial manifestaions of thalassemia major, protrusive premaxilla with flaring and spacing of the upper anterior teeth, increased overjet, reduced overbite, and prominent malar bones

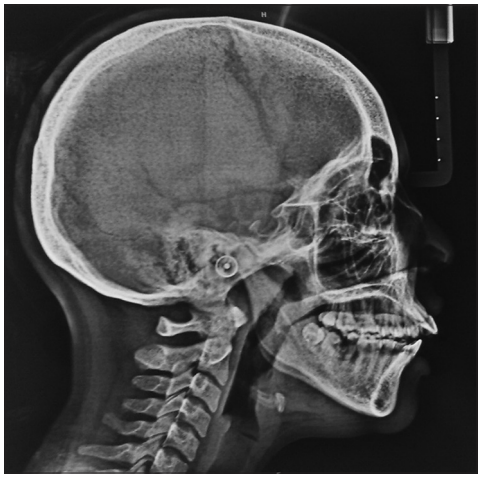

Figure 2: Typical cephalometric features of a Class II skeletal pattern

directly discrepancies in maxillary and mandibular length and relates them to the adult averages for the sex of the patient [Figure 4].[12]

Table 1: Cephalometric parameters defining craniofacial morphology

Measurement	Definition
SNA	Point A and anterior cranial base (S-N)
SNB	Point B and anterior cranial base
ANB	Point A, nasion, and point B
SNPog	Pogonion and anterior cranial base
ArGoM (gonial angle)	Points articulare, gonion, and menton
SN/MnP	Anterior cranial base and the mandibular plane
MxP/MnP	Maxillary plane and mandibular plane
SN/MxP	Anterior cranial base and maxillary plane
Y-axis/SN	Y-axis (S-Gn) and anterior cranial base
U1/MxP	Upper incisors and maxillary plane
L1/MnP	Lower incisors and mandibular plane
Nasolabial angle	Columella, subnasale, and labrale superius
PFH	Posterior face height (S-Go)
AFH	Anterior face height (N-Me)
S-N	Anterior cranial base length
S-Ar	Posterior cranial base length
Ar-Go	Ramus height
Go-Gn	Length of the mandibular body between gonion and gnathion
ANS-PNS	Length of the maxillary base between anterior nasal spine and (PNS)
S-N	Anterior cranial base length
U1□ MxP	Perpendicular distance of the incisal point of the upper incisor to the maxillary plane
L1□ MnP	Perpendicular distance of the incisal point of the lower incisor to the mandibular plane
U lip to E plane	Distance of the upper lip to E plane measured at the right angle From labial superius to E plane
L lip to E plane	the distance of the lower lip to E plane measured at the right angles From labial inferius to E plane
PFH: AFH	Percentage ratio between PFH and AFH

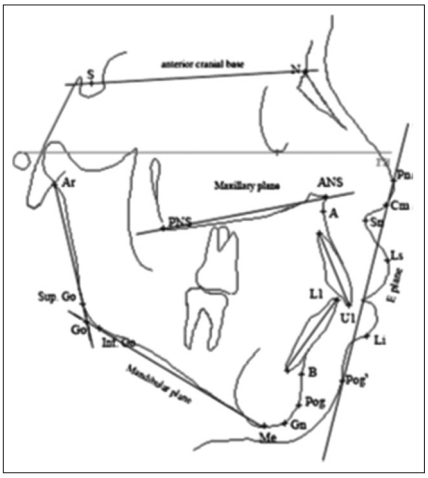

Figure 3: Cephalometric landmarks and planes

Third, 18 orthopantograms were taken for thalassemia patients ≤16 years of age for the analysis of dental development and compared with chronological age. Dental development, defined from the first appearance of calcified points to the apex closure, was assessed according to the method of Demirjian *et al*.[13] This method is one of the widely used methods for the estimation of DA. The seven left mandibular permanent teeth (second molar to central incisor) of each radiograph were rated on an eight-stage scale of dental development. The stages describe dental development from the first appearance of calcified points (Stage A) to the apex closure (Stage H). The sum of the scores for all the seven teeth was used to describe dental development, which was converted to DA using a conversion table and/or percentile curve. An example of determining DA using the Demirjian method is shown in Figure 5 and Table 2a-c.

Method error

For error evaluation, 15 cephalometric radiographs were randomly selected from both the thalassemia and the control groups and reevaluated after a 3-week interval by the same examiner. In addition, 10 orthopantograms were randomly selected for the thalassemia group and rescored by the same examiner. The differences between repeated measurements for cephalometric and panorama radiographs, using a paired *t*-test, to detect any systematic error showed no statistically significant differences ($P > 0.05$) for any of the measurements. The degree of reproducibility of measurements using the intraclass correlation coefficient, to detect any random error, showed excellent reproducibility with a minimum value of 0.878 and 0.679, respectively.

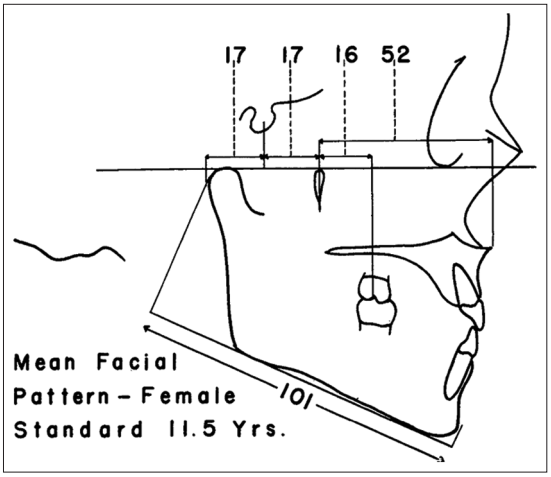

Figure 4: Wylie took several measurements on the Frankfort plane. These were as follows: The most posterior point on the mandibular condyle to Sella, Sella to pterygomaxillary fissure, pterygomaxillary fissure to the anterior nasal spine, and mandibular length. These landmarks were projected as perpendiculars to the Frankfort horizontal plane. According to Wylie, any of the first four dimensions, if larger than their respective mean value, will tend to make the face more orthognathic, and if less, they tend to make the face more prognathic

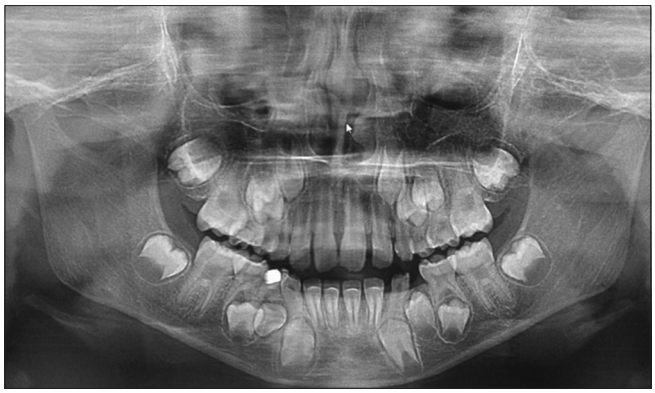

Figure 5: Panoramic radiograph of a boy with thalassemia aged 8.6 years used in the example of determining dental age in Table 2

Statistical analysis

Descriptive statistics, including the mean, standard deviation, and the difference between the means for each group (thalassemia and control), were analyzed using the Statistical Package for the Social Sciences version 15.0.1 (SPSS Inc., Chicago, ILL, USA). An independent *t*-test, with $P < 0.05$ set as the level of statistical significance, was used for the comparison of: (1) cephalometric measurements, angular and linear between thalassemia and control groups, and (2) DA with the chronological age of thalassemia patients' group.

RESULTS

The mean chronological age of the thalassemia and control groups was 12.9 ± 4.14 and 13.9 ± 3.96 years, respectively. The gender of thalassemia group was 18 males and 9 females, and for control group, it was 13 males and 15 females. The mean Hb level was 8.5 ± 1.1 g/dl.

General body growth

According to the standard growth charts of CDC for stature and weight, 59.3% and 51.9% of thalassemia group lie in the 3rd percentile, whereas 29.6% and 18.5% lie in the 10th percentile in stature and weight, respectively.

Cephalometric analysis

Comparison of cephalometric measurements between ß-thalassemia major patients and controls is shown in Table 3.

Skeletal

Neither group showed significant differences for SNA, whereas it showed significant differences in SNB, SNPog and Articular angles ($P < 0.05$), and a highly significant difference in ANB angle ($P < 0.005$) between the two groups. On the other hand, in the thalassemia group, angles related to mandibular plane inclination (SN/MnP and MxP/MnP angles) were significantly increased ($P < 0.005$) when compared with the controls. SN/Mxp also was significantly increased. Moreover, a significant reduction in the ratio of posterior to anterior face height was seen in the thalassemia group ($P < 0.005$). All linear skeletal measurements showed no significant differences between the two groups.

Compared to Wylie's standards, the cephalometric measurements showed that there was a maxillary prognathism about 18.8 mm in males and 14.5 in females in thalassemia patients [Table 4].

Dentoalveolar

The dentoalveolar relationship showed no differences between maxillary and mandibular teeth inclination (U1/MxP and L1/MnP) in relation to apical bases between both the groups. However, both the upper and lower incisors (U1⊥ MxP and L1⊥ MnP) had larger distances from their bases in thalassemia group than in controls. The upper incisors' distance to the maxillary base had a significant difference between the two groups ($P \leq 0.005$).

Table 2a: Determining the developmental stage of 7 left mandibular permanent teeth, from A to H. The stages represent development from first appearance of calcified points (stage A) to apex closure (stage H)

Type of tooth	Stage
M2	D
M1	G
P2	E
P1	E
C	F
I2	G
I1	G

Table 2b: Conversion of developmental stages to maturity scores for boys[13]

Type of tooth	A	B	C	D	E	F	G	H
M2	2.1	3.5	5.9	10.1	12.5	13.2	13.6	15.4
M1				8	9.6	12.3	17.0	19.3
P2	1.7	3.1	5.4	9.7	12.0	12.8	13.2	14.4
P1			3.4	7.0	11.0	12.3	12.7	13.5
C				3.5	7.9	10.0	11.0	11.9
I2				3.2	5.2	7.8	11.7	13.7
I1				0	1.9	4.1	8.2	11.8

Table 2c: A total dental maturity score of 80.0 is equivalent to a dental age of 8.6 years (according to the Demirjian method[13]), which is then compared to chronological age. In this example, No delay in dental development is present in a boy aged 8.6 years with thalassemia

Total dental maturity score
10.1+17.0+12.0+11.0+10.0+11.7+8.2=80.0.

Table 3: Comparison of cephalometric measurements between ß-thalassemia major patients and controls

	Thalassemia mean (SD) $n=27$		Control mean (SD) $n=28$		Sig. (2-tailed)	*t*-test	Level of significance
Skeletal							
SNA	81.33	3.922	80.36	3.684	0.346	0.952	NS
SNB	75.52	2.992	77.29	3.230	0.040	-2.103	*
ANB	5.81	3.126	3.21	1.524	0.000	3.899	**
SNPog (°)	75.58	3.313	78.00	3.103	0.008	-2.775	*
ArGoMe (°)	133.92	5.330	129.93	5.422	0.009	2.697	*
SN/MnP (°)	40.19	5.442	35.37	4.900	0.001	3.416	**
MxP/MnP (°)	34.70	5.703	25.93	5.650	0.000	0.5682	**
SN/MxP (°)	5.81	2.271	9.00	3.641	0.000	-3.907	**
PFH (mm)	58.44	6.077	61.29	5.091	0.067	-1.869	NS
AFH (mm)	96.35	8.890	94.68	8.255	0.478	0.715	NS
PFH: AFH (%)	60.4667	3.98690	64.7143	3.59894	0.000	-4.151	**
Y-axis/SN (°)	69.78	3.468	68.32	3.621	0.134	1.522	NS
NSAr (°)	122.70	4.952	122.86	6.687	0.924	-0.096	NS
S-N (mm)	57.96	4.254	56.39	4.669	0.198	1.302	NS
S-Ar (mm)	27.37	3.441	27.61	3.765	0.809	-0.243	NS
Ar-Go (mm)	34.78	4.368	36.79	3.425	0.063	-1.901	NS
Go-Gn (mm)	56.83	6.128	56.07	5.298	0.623	0.494	NS
ANS-PNS (mm)	43.04	3.028	42.61	3.489	0.628	0.487	NS
Dentoalveolar measurements							
U1/MxP (°)	109.08	6.170	110.96	7.346	0.313	-1.018	NS
L1/MnP (°)	96.15	6.987	95.14	5.655	0.559	0.588	NS
U1⊥ MxP (mm)	25.81	3.680	23.04	2.782	0.003	3.167	**
L1⊥ MnP (mm)	34.15	3.516	32.36	3.268	0.056	1.958	NS
Soft tissue measurements							
U lip to E plane	-1.5370	2.61992	-4.2679	2.60868	0.000	3.873	**
L lip to E plane	0.7593	2.20738	-1.7321	2.29525	0.000	4.101	**
Nasolabial angle (°)	93.48	10.009	100.89	13.785	0.027	-2.274	*

Table 4: Compareson between Wylie's standardsand cephalometric measurements

Measurement	Wylie standard (mm)		Sample Mean		Maxillary prognathism		Mandibular prognathism	
	M	F	M	F	M	F	M	F
Ar'-S'	18	17	12.0	13.4			6	3.6
S'-Ptm	18	17	17.1	17.3		0.3	0.9	
Ptm-ANS'	52	52	44.1	44.8			7.9	7.2
Ar'-P'	103	101	84.2	86.8	18.8	14.2		
Prognathism totals					18.8	14.5	14.8	10.8

Table 5: Correlation between dental age and chronological age

Age group $n=18$	CA mean	DA mean	Mean difference (DA minus CA)
5.0-7.0	5.7	6.3	0.6
7.1-9.0	8.4	8.9	0.5
9.1-11.0	10.5	9.8	-0.7
11.1-13.0	12.5	11.4	-1.1
13.1-16.1	15.2	15.1	-0.1

Soft tissue

Soft-tissue analysis revealed protrusion of the upper and lower lips ($P < 0.001$), with a significantly acute nasolabial angle ($P < 0.05$) in the thalassemia group.

Correlation between dental age and chronological age

Comparison of chronologic age and DA in patients with thalassemia major is shown in Table 5. Dental development in patients with ß-thalassemia major was significantly delayed relative to chronological age ($P < 0.001$) [Table 5].

DISCUSSION

Growth retardation was evident in all thalassemia age groups; the values, 74.1% and 55.6%, of the participants were less than the 10th percentiles of weight and height, respectively. The cause of growth retardation in children with ß-thalassemia major was reported in many studies; usually, it is multifactorial and includes chronic anemia and hypoxia, iron overload, low somatomedin activity, endocrinopathies, low-socioeconomic status, and racial factors.[9,11,14]

Cephalometrically, in this study, thalassemia patients exhibited a large intermaxillary distance (ANB) discrepancy that produced a skeletal Class II pattern. Başsimitçi *et al*. (1996), Abu Alhaija *et al*. (2002), and Amini *et al*. (2007) reported a significant increase in ANB angle in thalassemia major patients and attributed it to a short mandible. Although

cephalometrically, SNA, SNB, and ANB angles can give misleading results because they are affected by nasion (N) point, the results by Wylie's analysis confirmed that there is a maxillary prognathism in males and females of thalassemia group compared to Wylie's standards.

On the other hand, vertical (clockwise) rotation of the mandible in the thalassemia patients was consistent with previous studies and attributed to many factors, such as muscular weakness, mouth breathing, a larger articulare angle, as well as deficient condylar and ramus growth.[4-7,15,16]

Other studies showed that although more cancellous bone-containing marrow spaces in maxilla are present in thalassemia patients, there was no dramatic maxillary prognathism, but a normal inclination of upper incisors to the maxilla. The lower incisors' inclination is considered normal; they are considered proclined with an increase MxP/MnP angle.[17,18] Bassimitçi (1996) showed that anterior dentoalveolar height had a tendency to increase in thalassemia patients. The significant anterior (counterclockwise) rotation of the maxilla (SN/MxP) might possibly be interpreted as being due to enlargement of the maxillary marrow spaces. The soft-tissue analysis revealed significant ($P < 0.05$) elevation of the upper and lower lips together with an acute nasolabial angle in the thalassemia group. A depressed nose together with increased thickness of the upper lip might have contributed to the acute nasolabial angle as well as to the elevation of the upper and lower lips. These findings were consistent with Toman *et al*. (2011) but not with Amini *et al*. (2012). This can be explained that Amini *et al*. (2012) control group was Class II skeletal pattern, whereas Toman *et al*. (2011) study, like our present one, is Class I skeletal pattern.

There was a significant delay in dental development with advancing age. Furthermore, there was a significant correlation ($P < 0.001$) between the extent of this delay and chronological age, which indicates that the delay increases, as the patient gets older. Studies have shown a low correlation between dental maturity and physical development, which suggests that dental development is less influenced than somatic development by environmental factors. Hattab (2013) suggested that pediatric dentists and orthodontists must be mindful of both the growth patterns associated with thalassemia and the effects that delays in dental development have on diagnosis and treatment timing.

Clinical relevance

Almost all of the craniofacial features of ß-thalassemia major patients and their delay in dental development are of orthodontic concern, and therefore, it is important to understand the changes associated with ß-thalassemia major and their implications for orthodontic treatment. In addition, this study sheds a light on the multidisciplinary roles of the orthodontists, the pediatric dentists, and the other relevant medical specialties in the management of ß-thalassemia major patients.

CONCLUSIONS

β-thalassemia major manifestations increase with extramedullary hematopoiesis along the years. Craniofacial malformations and dental malocclusions tend to be less intense with early medical care. Therefore, a proper orthodontic care should be delivered through a coordinated team approach, with the hematologist, pediatrician, and a pediatric dentist to undertake a complete risk assessment for every single patient. Orthodontic interceptive treatment is crucial in controlling the skeletal changes such as improper craniofacial growth. It is comprised maxillary orthopedic treatment directed toward the maxilla, and mandibular modification by functional appliances followed by fixed orthodontic treatment. Such early orthodontic intervention prevents future two-jaw orthognathic surgery to control skeletal and dental malformations in all dimensions. The clinician should keep in mind that due to thinner cortical plates' low force magnitude, nonextraction orthodontic treatment planning combined with close orthodontic follow-up should be applied to minimize risk for these patients. Radiographs at 3-month intervals can be indispensable. Furthermore, infection control protocol for high-risk patients should be performed because these patients are at high risk of HIV and hepatitis B and C infections. Functional and extraoral appliances when used, the "skeletal forces" must be less than what is used with normal patients.[19]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Weatherall DJ, Clegg JB. The Thalassaemia Syndromes. Oxford:

Blackwell Science; 2001.
2. Cannell H. The development of oral and facial signs in beta-thalassaemia major. Br Dent J 1988;164:50-1.
3. Hes J, van der Waal I, de Man K. Bimaxillary hyperplasia: The facial expression of homozygous beta-thalassemia. Oral Surg Oral Med Oral Pathol 1990;69:185-90.
4. Başsimitçi S, Yücel-Eroğlu E, Akalar M. Effects of thalassaemia major on components of the craniofacial complex. Br J Orthod 1996;23:157-62.
5. Abu Alhaija ES, Hattab FN, al-Omari MA. Cephalometric measurements and facial deformities in subjects with beta-thalassaemia major. Eur J Orthod 2002;24:9-19.
6. Amini F, Jafari A, Eslamian L, Sharifzadeh S. A cephalometric study on craniofacial morphology of Iranian children with beta-thalassemia major. Orthod Craniofac Res 2007;10:36-44.
7. Toman HA, Nasir A, Hassan R, Hassan R. Skeletal, dentoalveolar, and soft tissue cephalometric measurements of Malay transfusion-dependent thalassaemia patients. Eur J Orthod 2011;33:700-4.
8. Flynn DM, Fairney A, Jackson D, Clayton BE. Hormonal changes in thalassaemia major. Arch Dis Child 1976;51:828-36.
9. Saxena A. Growth retardation in thalassemia major patients. Int J Hum Genet 2003;3:237-46.
10. Hazza'a AM, Al-Jamal G. Dental development in subjects with thalassemia major. J Contemp Dent Pract 2006;7:63-70.
11. Hattab FN. Patterns of physical growth and dental development in Jordanian children and adolescents with thalassemia major. J Oral Sci 2013;55:71-7.
12. Wylie WL. The assessment of antero-posterior dysplasia. Angle Orthod 1947;17:97-109.
13. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Hum Biol 1973;45:211-27.
14. Laor E, Garfunkel A, Koyoumdjisky-Kaye E. Skeletal and dental retardation in beta-thalassemia major. Hum Biol 1982;54:85-92.
15. Baker DH. Roentgen manifestations Cooley's anemia. Ann N Y Acad Sci 1964;119:641-61.
16. Asbell MB. Orthodontic aspects of Cooley's anemia. Ann N Y Acad Sci 1964;119:662-3.
17. Johnston FE, Krogman WM. Patterns of growth in children with thalassemia major. Ann N Y Acad Sci 1964;119:667-79.
18. Amini F, Borzabadi-Farahani A, Mashayekhi Z, Pousti M, Amirtouri M. Soft-tissue profile characteristics in children with beta thalassaemia major. Acta Odontol Scand 2013;71:1071-6.
19. Einy S, Hazan-Molina H, Ben-Barak A, Aizenbud D. Orthodontic consideration in patients with beta-thalassemia major: Case report and literature review. J Clin Pediatr Dent 2016;40:241-6.