European Journal of Orthodontics 33 (2011) 700–704
doi:10.1093/ejo/cjq147
Advance Access Publication 31 January 2011

Skeletal, dentoalveolar, and soft tissue cephalometric measurements of Malay transfusion-dependent thalassaemia patients

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SUMMARY Thalassaemia is a public health problem in Malaysia. It is known to cause skeletal deformity. The purpose of this study was to compare the skeletal, dentoalveolar, and soft tissue features of Malay transfusion-dependent thalassaemia (TDT) patients with a Malay control group. Lateral cephalometric radiographs of 30 Malay (14 males and 16 females aged 6.4–21.8 years) TDT patients and 60 normal Malays matched for chronological age and gender were analysed and compared using an independent *t*-test.

The TDT group showed a similar sagittal relationship to the control group but with a significantly increased ($P < 0.01$) mandibular plane inclination. They also showed a significantly shorter ($P \leq 0.001$) mandibular body, ramus length, and posterior face height and consequently a smaller ratio of posterior to anterior face height ($P < 0.01$). The upper and lower lips were significantly procumbent ($P < 0.001$) in the TDT group together with a significantly smaller nasolabial angle ($P < 0.05$). Dentoalveolar measurements showed less proclined maxillary teeth in the TDT group compared with the controls ($P < 0.05$). The cephalometric features of Malay TDT patients were characterized by a mild Class II skeletal pattern, prominent vertical growth direction of the mandible, and protruded upper and lower lips.

Introduction

Thalassaemia is a genetic disease characterized by absent or deficient synthesis of one or more of the globin chain subunits of haemoglobin (Weatherall and Clegg, 2001). Abnormal globin chain synthesis leads to anaemia, ineffective erythropoiesis, and subsequent erythroid hyperplasia, which result in expansion of the bone marrow and secondary skeletal and craniofacial deformity, mainly seen in poorly treated patients (Mohamed and Jackson, 1998; Tyler *et al.*, 2006).

The craniofacial features of thalassaemia have been described in several reports. However, these were mainly based on observation (Poyton and Davey, 1968; Jackson *et al.*, 1987; Cannell, 1988; Hes *et al.*, 1990). Pusaksrikit *et al.* (1987a,b) investigated the facial skeletal profiles and pattern of dental occlusion in a group of Thai thalassaemia patients. Those studies showed that a facial skeletal Class II was more common in the thalassaemia group than in the control group and that the occlusal pattern in thalassaemia patients was different from a normal population. In both studies, a Class III dental malocclusion and facial skeletal pattern were not found in thalassaemia patients.

To date, there are limited investigations involving thalassaemia patients. The first comprehensive orthodontic cephalometric study was undertaken in Turkey (Bassimitci *et al.*, 1996) followed by Jordanian (Abu Alhaija *et al.*, 2002) and Iranian (Amini *et al.*, 2007) studies. All these investigations were undertaken on β-thalassaemia major patients. Their findings showed that the typical craniofacial features of β-thalassaemia major subjects were 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.

Thalassaemia is considered a public health problem in south-east Asian countries, where in some parts the carrier rate reaches 60 per cent (Fucharoen *et al.*, 2004; Vichinsky, 2005; Ismail *et al.*, 2006). In Malaysia, about 120–350 patients are born each year with thalassaemia (Malaysian Health Technology Assessment Unit, 2003). At present, no comprehensive cephalometric study from this area has been carried out. Thus, the aim of this research study was to analyse the cephalometric characteristics of Malay transfusion-dependent thalassaemia (TDT) patients and to compare them with a Malay control group.

Subjects and methods

A case–control study was conducted at the Dental Clinic and Paediatric Day Care Centre, Hospital Universiti Sains

Malaysia (HUSM). This study was approved by the Research Ethics Committee (Human), USM (USMKK/PPP/JEPeM [198.4(2.2)]). The diagnosis of thalassaemia was made based on high-performance liquid chromatography and haemoglobin electrophoresis. Of the 52 registered thalassaemia patients 30 (14 males and 16 females, aged 6.4–21.8 years) agreed to participate in the study. The inclusion criteria were Malay TDT patients who received at least two blood transfusions per year that started 12 months prior the study. Patients who had orthodontic treatment or any other acquired or congenital craniofacial deformity were excluded. Every TDT patient was matched with two control subjects according to ethnicity, chronological age (±1 year), and gender. The control cephalometric radiographs were of 60 subjects with a Class I malocclusion, no previous orthodontic treatment, and no developmental or acquired craniofacial deformity. In both groups, no significant difference between males and females was detected; therefore, measurements for both genders were pooled.

Lateral cephalometric radiographs were obtained for the TDT patients with an Orthoralix (Gendex Dental Systems, Des Plaines, Illinois, USA) using a standardized technique with the ear rods in the external auditory meatus, the mandible in centric occlusion, and the lips in a relaxed position. For the control group, the radiographs were obtained from pre-treatment records of orthodontic patients, attending HUSM. All radiographs were analysed with CASSOS 2001 software (Computer Assisted Simulation System for Orthognathic Surgery, Hong Kong) by a single operator (HAT). A customized analysis that was a combination of Jarabak, Burstone, COGS (Athanasiou, 1995), and Eastman (Mitchell, 2001) analyses was used. Twenty-five linear and angular measurements were chosen to analyse the differences in both groups (Table 1). The landmarks and planes used in this analysis are shown in Figure 1.

Table 1 Cephalometric measurements.

Measurements	Definition
Angular	
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
NSAr (saddle angle)	Between points nasion, sella, and articulare
U1/MxP	Upper incisors and maxillary plane
L1/MnP	Lower incisors and mandibular plane
Nasolabial angle	Columella, subnasale, and labrale superius
Linear	
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)
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	The distance of the upper lip to E plane measured at the right angle from labrale superius to E plane
L lip to E plane	The distance of the lower lip to E plane measured at the right angles from labrale inferius to E plane
PFH:AFH	Percentage ratio between PFH and AFH

Method error

For error evaluation, 15 cephalometric radiographs were randomly selected from both the TDT and the control groups and re-evaluated after a 2 week interval by the same examiner. The differences between repeated measurements, using a paired *t*-test, to detect any systematic error showed no significant differences ($P > 0.05$) for any of the measurements. The degree of reproducibility of measurements using intraclass correlation coefficient, to detect any random error, showed excellent reproducibility with a minimum value of 0.749.

Statistical analysis

Descriptive statistics, including the mean, standard deviation (SD), and difference between the means for each group, were analysed using the Statistical Package for Social Sciences version 12.0.1(SPSS Inc., Chicago, Illinois, USA). An independent *t*-test was used for the comparison of cephalometric measurements, with $P < 0.05$ set as the level of significance.

Results

The TDT group comprised 3 patients with β-thalassaemia major (10 per cent), 24 with Hb E/β-thalassaemia (80 per cent), 2 with Hb H Constant Spring (6.7 per cent), and 1 with Hb H disease (3.3 per cent). Their mean haemoglobin level was 6.5 ± 0.60 g/dl. The mean chronological age of the TDT and control groups was 12.7 ± 4.56 and 12.8 ± 4.48 years, respectively. Among TDT patients less than 18 years of age (25 of 30), 43.3 and 46.7 per cent were below the third percentile of height and weight, respectively. The results of the cephalometric analysis are shown in Table 2.

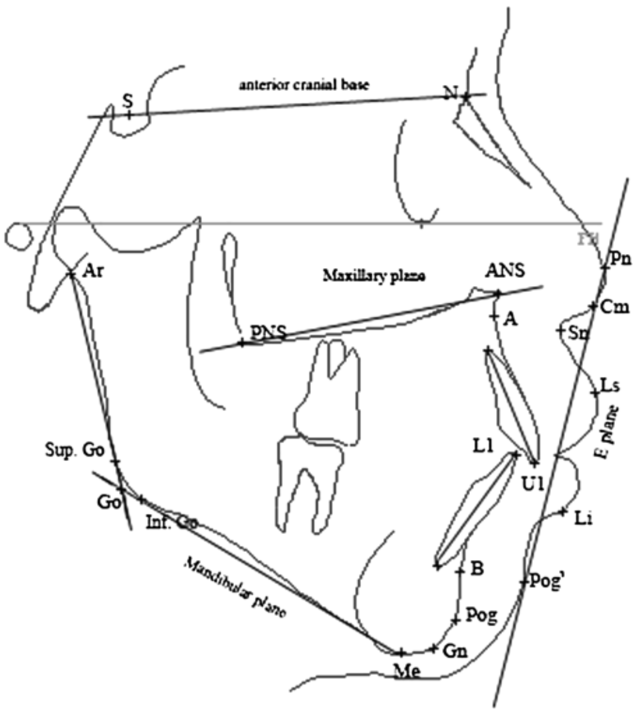

Figure 1 Cephalometric landmarks and planes. N = nasion, the most anterior point of the frontonasal suture in the midsagittal plane; S = midpoint of sella (the centre of sella turcica); Ar = articulare, a point at the intersection of the image of the posterior margin of the ramus and the outer margin of the cranial base; Go = gonion, a point at the intersection of lines tangent to the posterior border of the ramus (articulare–superior gonion; Sup. Go) and the lower border of the mandible (menton–inferior gonion; Inf. Go); Me = menton, the most inferior point of the outline of the symphysis in the midsagittal plane; Gn = gnathion, the most anterior inferior point of the bony chin; Pog = pogonion, the most anterior point of the bony chin in the midsagittal plane; B = point B, supramentale, the deepest point on the outer contour of the mandible; A = point A, subnasale, the deepest midline point on the anterior outer contour of the maxillary alveolar process; ANS = anterior nasal spine, the most anterior point of the tip of the anterior nasal spine in the midsagittal plane; PNS = posterior nasal spine; L1 = lower incisal constructed between incisal tip of most anterior mandibular central incisor and its apex; U1 = upper incisor constructed between incisal tip of most anterior maxillary central incisor and its apex; Pog' = soft tissue pogonion, the most anterior point on the soft tissue chin; Li = labrale inferius, the muco-cutaneous border of the lower lip; Ls = labrale superius, a point on the muco-cutaneous junction of upper lip and philtrum; Sn = subnasale, a point at which the nasal septum merges with the upper cutaneous lip in the midsagittal plane; Cm = columella, the most anterior point on the columella of the nose; Pn = pronasale, the most prominent point on the tip of the nose. Maxillary plane = a plane running through ANS and PNS; mandibular plane = a plane running through points Me and Go; E plane = a plane running through points Pn and Pog'.

Skeletal

Neither group showed significant differences ($P > 0.05$) for any sagittal variables (SNA, SNB, ANB, and SNPog angles). On the other hand, in the TDT group, all angles related to mandibular plane inclination (ArGoMe, SN/MnP, and MxP/MnP angles) were significantly increased ($P < 0.01$) when compared with the controls. Moreover, a significant reduction in posterior face height and in the ratio of posterior to anterior face height was seen in the TDT group ($P < 0.01$). TDT patients showed a significantly shorter mandibular body and ramus length ($P \leq 0.001$), while maxillary length was insignificantly different. Posterior cranial base length was shorter in the TDT group ($P < 0.01$). There was no difference in any other cranial base measurements in either group.

Dentoalveolar

The dentoalveolar relationship showed retroclined maxillary teeth in the TDT group compared with the control group ($P < 0.05$) while the mandibular teeth had a similar inclination in both groups. However, both upper and lower incisors were nearly at the same distance from their bases in both groups (U1⊥ MxP and L1⊥ MnP).

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 TDT group.

Discussion

The results of the present research are in agreement with previous studies on the main features of thalassaemia (Bassimitci *et al.*, 1996, Abu Alhaija *et al.*, 2002, Amini *et al.*, 2007). These features include a vertical growth direction of the mandible, a short mandibular body, a short ramus length, and eversion of the upper and lower lips. However, the TDT patients showed a slight increase in ANB angle compared with the control group. Bassimitci *et al.* (1996), Abu Alhaija *et al.* (2002), and Amini *et al.* (2007) reported a significant increase in ANB angle in thalassaemia major patients and attributed it to a short mandible (Abu Alhaija *et al.*, 2002; Amini *et al.*, 2007) and posterior cranial base (Abu Alhaija *et al.*, 2002), as well as vertical rotation of the mandible (Amini *et al.*, 2007). Despite the presence of such factors, a Class II skeletal pattern was not prominent in the TDT patients in the present study. This could be explained by the anterior (anticlockwise) rotation of the maxilla in the TDT group as indicated by a smaller ($P > 0.05$) SN/MxP angle, which might counteract maxillary prognathism. Another important factor is the position of point nasion that could be affected by a depressed nasal bridge or prominent frontal bone, which are common in thalassaemia patients. In general, this is consistent with the findings of Pusaksrikit *et al.* (1987a) that the skeletal pattern of thalassaemia patients is limited to Classes I and II.

On the other hand, vertical (clockwise) rotation of the mandible in the thalassaemia patients is consistent with previous studies (Bassimitci *et al.*, 1996; Abu Alhaija *et al.*, 2002; Amini *et al.*, 2007). This finding has been attributed to many factors, such as muscular weakness (Logothetis *et al.*, 1971), mouth breathing, and a larger articulare angle (Bassimitci *et al.*, 1996) as well as deficient condylar and ramus growth (Amini *et al.*, 2007).

Table 2 Comparison of cephalometric measurements between the transfusion-dependent thalassaemia (TDT) subjects and controls.

Variable	TDT, mean (SD), $n = 30$	Control, mean (SD), $n = 60$	Mean difference (95% CI)	t statistic (df)	P value	Level of significance
Age (years)	12.7 (4.56)	12.7 (4.48)	0.09 (−1.9 to 2.0)	0.94 (88)	0.925	NS
Skeletal measurements						
SNA (°)	88.2 (5.43)	88.2 (5.29)	−0.03 (−2.4 to 2.3)	−0.02 (88)	0.981	NS
SNB (°)	84.0 (4.86)	84.9 (5.33)	0.97 (−1.3 to 3.3)	0.84 (88)	0.405	NS
ANB (°)	4.3 (2.74)	3.3 (3.14)	−0.92 (−2.3 to 0.4)	−1.37 (88)	0.175	NS
SNPog (°)	83.8 (4.91)	85.1 (5.39)	1.28 (−1.1 to 3.6)	1.10 (88)	0.276	NS
ArGoMe (°)	131.3 (6.51)	127.0 (5.53)	−4.31(−6.9 to −1.7)	−3.28 (88)	0.001	***
SN/MnP (°)	33.7 (6.16)	29.7 (6.16)	−3.97(−6.7 to −1.2)	−2.88 (88)	0.005	**
MxP/MnP (°)	34.1 (5.35)	29.1 (5.11)	−4.93 (−7.2 to −2.6)	−4.25 (88)	<0.001	***
SN/MxP (°)	−0.4 (4.01)	0.6 (4.65)	0.97 (−1.0 to 2.9)	0.97 (88)	0.335	NS
PFH (mm)	69.9 (5.87)	75.8 (8.94)	5.91 (2.8 to 9.0)	3.75 (81)	<0.001	***
AFH (mm)	111.4 (10.72)	113.5 (9.42)	2.10 (−2.3 to 6.5)	0.95 (88)	0.343	NS
PFH:AFH (%)	63.0 (5.33)	67.0 (5.64)	3.78 (1.3 to 6.2)	3.05 (88)	0.003	**
Y-axis/SN (°)	64.7 (3.57)	63.5 (4.64)	−1.23 (−3.2 to 0.7)	−1.28 (88)	0.205	NS
S–N (mm)	66.5 (4.51)	66.9 (4.46)	0.44 (−1.6 to 2.4)	0.44 (88)	0.663	NS
S–Ar (mm)	31.9 (3.51)	34.4 (4.20)	2.48 (0.7 to 4.3)	2.78 (88)	0.007	**
NSAr (°)	115.1 (6.26)	116.1 (6.50)	1.09 (−1.8 to 3.9)	0.76 (88)	0.452	NS
Ar–Go (mm)	40.9 (4.10)	44.8 (6.50)	3.88 (1.6 to 6.1)	3.44 (83)	0.001	***
Go–Gn (mm)	70.5 (5.84)	76.9 (8.13)	6.40 (3.4 to 9.4)	4.28 (77)	<0.001	***
ANS–PNS (mm)	48.5 (4.88)	48.1 (4.63)	−0.44 (−2.5 to 1.7)	−0.42 (88)	0.676	NS
Dentoalveolar measurements						
U1/MxP (°)	113.6 (7.99)	119.5 (6.92)	5.85 (2.6 to 9.1)	3.59 (88)	0.001	***
L1/MnP (°)	95.7 (7.17)	96.0 (7.69)	0.32 (−3.0 to 3.7)	0.19 (88)	0.851	NS
U1⊥ MxP (mm)	30.5 (5.45)	29.2 (3.43)	−1.37 (−3.6 to 0.8)	−1.26 (41)	0.216	NS
L1⊥ MnP (mm)	39.3 (5.22)	40.2 (4.52)	0.92 (−1.2 to 3.0)	0.87 (88)	0.388	NS
Soft tissue measurements						
U lip to E plane	4.3 (2.33)	0.3 (2.72)	−4.02 (−5.2 to −2.9)	−6.92 (88)	<0.001	***
L lip to E plane	5.8 (3.12)	2.1 (2.85)	−3.74 (−5.0 to −2.4)	−5.69 (88)	<0.001	***
Nasolabial angle (°)	87.2 (17.05)	96.8 (16.51)	9.55 (2.1 to 17.0)	2.56 (88)	0.012	**

NS = not significant. **$P < 0.01$, ***$P < 0.001$.

The findings of the present study suggest that a short ramus could be the main contributing factor. In fact, a reduced ramus height and mandibular body length in the TDT group could be due to general growth retardation and impaired puberty. In this study, nearly half of the TDT patients were below the third percentile in height and weight. As documented by Baccetti *et al.* (2002), the mandible has a growth spurt that is related to total body growth and puberty. Y-axis/SN and MnP/SN angles suggest that the unfavourable growth pattern in thalassaemia patients could be due to deficient condylar growth (Schudy, 1968).

There was no significant difference in dentoalveolar measurements in either group except that the upper incisors in the TDT patients were less proclined ($P < 0.05$). This indicates that the feature of prominent maxillary anterior teeth described by Cannell (1988) and Hes *et al.* (1990) is not common in Malay TDT patients but is consistent with the finding of Abu Alhaija *et al.* (2002). Furthermore, bimaxillary proclination of upper and lower incisors is common among the Asian population (Lamberton *et al.*, 1980; Lew, 1989; Tan, 1996).

Soft tissue analysis revealed significant ($P < 0.05$) elevation of the upper and lower lips together with an acute nasolabial angle in the TDT group. The morphology of the nasolabial angle is affected by the maxilla, maxillary teeth, nasal tip, and thickness of the upper lip (Sarver, 1998). In this study, the antero-posterior position of the maxilla or maxillary tooth angulation could not explain the acute nasolabial angle in the TDT group; neither was found to be prominent. However, 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. In general, the cephalometric measurements suggest that the craniofacial deformity of these TDT patients was mainly due to mandibular growth retardation.

Conclusions

Cephalometric features of Malay TDT patients compared with normal controls are a mild Class II skeletal pattern, a prominent vertical growth direction of the mandible, protruded upper and lower lips, and less proclined upper incisors.

Funding

Universiti Sains Malaysia Short Term(304/PPSG/6139016).

Acknowledgements

Our appreciation goes to the thalassaemia patients and their parents for their co-operation, Dr Wan M. Zahiruddin for his assistance with the statistical analysis, and Prof. Faridah Abdul Rashid for help in manuscript editing.

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