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 ≤ 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). Pusaksricket 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 standardised 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.

**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.

**Descriptive 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.
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 \( (U1 \perp MxP \text{ and } L1 \perp MnP) \).

**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 \( (\text{Bassimicitci et al., 1996, Abu Alhaija et al., 2002, Amini et al., 2007}) \). 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. \( \text{Bassimicitci et al. (1996), Abu Alhaija et al. (2002), and Amini et al. (2007)} \) reported a significant increase in ANB angle in thalassaemia major patients and attributed it to a short mandible \( (\text{Abu Alhaija et al., 2002; Amini et al., 2007}) \) and posterior cranial base \( (\text{Abu Alhaija et al., 2002}) \), as well as vertical rotation of the mandible \( (\text{Amini et al., 2007}) \). 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 \( \text{Pusaksritik et al. (1987a)} \) 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 \( (\text{Bassimicitci et al., 1996; Abu Alhaija et al., 2002; Amini et al., 2007}) \). This finding has been attributed to many factors, such as muscular weakness \( (\text{Logothetis et al., 1971}) \), mouth breathing, and a larger articulare angle \( (\text{Bassimicitci et al., 1996}) \) as well as deficient condylar and ramus growth \( (\text{Amini et al., 2007}) \).
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 group could be due to general growth retardation and reduced ramus height and mandibular body length in the ramus could be the main contributing factor. In fact, a short ramus could be due to general growth retardation. The morphology of the nasolabial angle is affected by the maxilla, maxillary teeth, nasal tip, and thickness of the upper lip (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 (Schurer, 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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>TDT, mean (SD), ( n = 30 )</th>
<th>Control, mean (SD), ( n = 60 )</th>
<th>Mean difference (95% CI)</th>
<th>( t ) statistic (df)</th>
<th>( P ) value</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12.7 (4.56)</td>
<td>12.7 (4.48)</td>
<td>0.09 (−1.9 to 2.0)</td>
<td>0.94 (88)</td>
<td>0.925</td>
<td>NS</td>
</tr>
<tr>
<td>Skeletal measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNA (°)</td>
<td>88.2 (5.43)</td>
<td>88.2 (5.29)</td>
<td>−0.03 (−2.4 to 2.3)</td>
<td>−0.02 (88)</td>
<td>0.981</td>
<td>NS</td>
</tr>
<tr>
<td>SNB (°)</td>
<td>84.0 (4.86)</td>
<td>84.9 (5.33)</td>
<td>0.97 (−1.3 to 3.3)</td>
<td>0.84 (88)</td>
<td>0.405</td>
<td>NS</td>
</tr>
<tr>
<td>ANB (°)</td>
<td>4.3 (2.74)</td>
<td>3.3 (3.14)</td>
<td>−0.92 (−2.3 to 0.4)</td>
<td>−1.37 (88)</td>
<td>0.175</td>
<td>NS</td>
</tr>
<tr>
<td>SNbGoMe (°)</td>
<td>83.8 (9.91)</td>
<td>85.1 (5.39)</td>
<td>1.28 (−1.1 to 3.6)</td>
<td>1.10 (88)</td>
<td>0.276</td>
<td>NS</td>
</tr>
<tr>
<td>ArGoMe (°)</td>
<td>131.3 (6.51)</td>
<td>127.0 (5.53)</td>
<td>−4.31 (−6.9 to −1.7)</td>
<td>−3.28 (88)</td>
<td>0.001</td>
<td>***</td>
</tr>
<tr>
<td>SN/MnP (°)</td>
<td>33.7 (6.16)</td>
<td>29.7 (6.16)</td>
<td>−3.97 (−6.7 to −1.2)</td>
<td>−2.88 (88)</td>
<td>0.005</td>
<td>**</td>
</tr>
<tr>
<td>MxP:MnP (°)</td>
<td>34.1 (5.35)</td>
<td>29.1 (5.11)</td>
<td>−4.93 (−7.2 to −2.6)</td>
<td>−4.25 (88)</td>
<td>&lt; 0.001</td>
<td>***</td>
</tr>
<tr>
<td>SN/MxP (°)</td>
<td>−0.4 (4.01)</td>
<td>0.6 (4.65)</td>
<td>0.97 (−1.0 to 2.9)</td>
<td>0.97 (88)</td>
<td>0.335</td>
<td>NS</td>
</tr>
<tr>
<td>PFH (mm)</td>
<td>69.9 (5.87)</td>
<td>75.8 (8.94)</td>
<td>5.91 (2.8 to 9.0)</td>
<td>3.75 (81)</td>
<td>&lt; 0.001</td>
<td>***</td>
</tr>
<tr>
<td>AFH (mm)</td>
<td>111.4 (10.72)</td>
<td>113.5 (9.42)</td>
<td>2.10 (−2.3 to 6.5)</td>
<td>0.95 (88)</td>
<td>0.343</td>
<td>NS</td>
</tr>
<tr>
<td>PFH:AFH (%)</td>
<td>63.0 (5.33)</td>
<td>67.0 (5.64)</td>
<td>3.78 (1.3 to 6.2)</td>
<td>3.05 (88)</td>
<td>0.003</td>
<td>**</td>
</tr>
<tr>
<td>Y-axis/SN (°)</td>
<td>64.7 (3.57)</td>
<td>63.5 (4.64)</td>
<td>−1.23 (−3.2 to 0.7)</td>
<td>−1.28 (88)</td>
<td>0.205</td>
<td>NS</td>
</tr>
<tr>
<td>S–N (mm)</td>
<td>66.5 (4.51)</td>
<td>66.9 (4.46)</td>
<td>0.44 (−1.6 to 2.4)</td>
<td>0.44 (88)</td>
<td>0.663</td>
<td>NS</td>
</tr>
<tr>
<td>S–Ar (mm)</td>
<td>31.9 (3.51)</td>
<td>34.4 (4.20)</td>
<td>2.48 (0.7 to 4.3)</td>
<td>2.78 (88)</td>
<td>0.007</td>
<td>**</td>
</tr>
<tr>
<td>NSAr (°)</td>
<td>115.1 (6.26)</td>
<td>116.1 (6.50)</td>
<td>1.09 (−1.8 to 3.9)</td>
<td>0.76 (88)</td>
<td>0.452</td>
<td>NS</td>
</tr>
<tr>
<td>Ar–Go (°)</td>
<td>40.9 (4.10)</td>
<td>44.8 (6.50)</td>
<td>3.88 (1.6 to 6.1)</td>
<td>3.44 (83)</td>
<td>0.001</td>
<td>***</td>
</tr>
<tr>
<td>Go–Gn (mm)</td>
<td>70.5 (5.84)</td>
<td>76.9 (8.13)</td>
<td>6.40 (3.4 to 9.4)</td>
<td>4.28 (77)</td>
<td>&lt; 0.001</td>
<td>***</td>
</tr>
<tr>
<td>ANS–PNS (mm)</td>
<td>48.5 (4.88)</td>
<td>48.1 (4.63)</td>
<td>−0.44 (−2.5 to 1.7)</td>
<td>−0.42 (88)</td>
<td>0.676</td>
<td>NS</td>
</tr>
</tbody>
</table>

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.L. MxP (mm) | 30.5 (5.45) | 29.2 (3.43) | −1.37 (−3.6 to 0.8) | −1.26 (41) | 0.216 | NS |
| L1.L. 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. **\( P < 0.01 \), ***\( P < 0.001 \).
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