CRANIOFACIAL DEFORMITIES IN TRANSFUSION-DEPENDENT THALASSEMIA PATIENTS IN MALAYSIA: PREVALENCE AND EFFECT OF TREATMENT

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Abstract. This comparative cross-sectional study was conducted in the pediatric daycare unit, Hospital Universiti Sains Malaysia to determine the prevalence of craniofacial deformities (CFD) and the association between these deformities and different clinical presentations among thalassemia patients. Patients were classified as either craniofacial deformity positive (CFD+) or craniofacial deformity negative (CFD-) by two examiners based on the presence or absence of deformity of the cheeks, frontal and/or maxillary bones. Fifteen clinical parameters were compared between the groups. Nineteen out of 43 patients (44.2%; confidence interval, 30.2-58.2%) had craniofacial deformities (CFD+). Both groups were comparable among the clinical parameters studied. Patients in the CFD+ group did not start their blood transfusions significantly earlier than the CFD- group (p=0.50) and had a nonsignificantly lower mean pretransfusion hemoglobin level than the CFD- group (p=0.71). Patients receiving regular monthly blood transfusions had a nonsignificantly smaller percentage of CFD than those transfused less often (p=0.495). CFD+ patients had a splenectomy at a nonsignificantly younger age than CFD- patients (p=0.36). HbE/β thalassemia patients were not significantly less likely to develop CFD than other varieties (p=0.50) and males had a nonsignificantly higher percentage of CFD than females (p=0.29). This study shows CFD in thalassemia patients are still prevalent but no significant associated factors were found; however, a nonsignificantly higher prevalence of CFD was observed in patients with signs of severe disease and less efficient treatment.

Keywords: craniofacial deformity, thalassemia, Malaysia

INTRODUCTION

The clinical features of severe thalassemia were first described in 1925 by Thomas Cooley: gross skeletal deformities, growth retardation and massive enlargement of the spleen and liver; these remained unchanged until the early 1960s (Weatherall and Clegg, 2001). However, with the use of frequent blood transfusions, the picture has changed dramatically, reducing the effects of ineffective erythropoiesis and its subsequent complications (Orzincolo *et al*, 1994; Chan *et al*, 2002). It has also reduced the risk of bone deformities (Karagiorga-Lagana *et al*,

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1987). Patients diagnosed with more severe forms of thalassemia and not receiving regular blood transfusions suffer more from anemia related complications (Mohamed and Jackson, 1998).

The craniofacial features of β-thalassemia major include prominent cheekbones and a protrusive premaxilla with distinct depression of the bridge of the nose, described as "rodent" or "chipmunk" faces (Canell, 1988; Bassimitci *et al*, 1996; Abu Alhaija *et al*, 2002). A "chipmunk face" mainly involves the maxillary area and has overgrowth in all directions and protrusion of the exposed anterior teeth. In some patients, a milder deformity described as "mongoloid face" characterized by prominent frontal and parietal bones, sunken nasal bridge, depressed zygomas and upward slant of the eyes is present (Jackson *et al*, 1987; Abu Alhaija *et al*, 2002).

Various factors, such as patient age, duration of clinical symptoms, degree of anemia, timing of splenectomy and age at onset of transfusion therapy, were important in determining the development of craniofacial deformities (Logothetis *et al*, 1971). These factors were used in some studies to grade the severity of thalassemia, especially Hb E/β thalassemia (Phadke and Agarwal, 2003; Sripichai *et al*, 2008).

In Malaysia, of 4,541 thalassemia affected patients, nearly 73% presented with transfusion-dependent β-thalassemia major or HbE/ β-thalassemia, 10% with thalassemia intermedia, 9% with HbH disease and the rest with other types of thalassemia (Malaysian Health Technology Assessment, 2009).

There is limited data on craniofacial deformities (CFD) among transfusion-dependent thalassemia (TDT) patients. Therefore, this study was conducted to determine the prevalence of craniofacial deformities among transfusion-dependent thalassemia patients and their association with different clinical aspects.

MATERIALS AND METHODS

We conducted a cross-sectional study at the Pediatric Day Care Unit, Hospital Universiti Sains Malaysia from January 2008 to June 2008. Malay transfusion-dependent thalassemia (TDT) patients who started regular blood transfusions twelve months or more before the study with at least two transfusions per year were eligible to participate. All those who signed the consent form were enrolled in the study.

Frontal and lateral photographs of the TDT patients were taken at a distance of 150 cm from the patient for standardization with a SONY Cyber-shot DSC-S650 digital still camera. The photographs were evaluated by two trained examiners (dentist) and (pediatrician). Patients with bony deformities in the form of frontal bossing and/or bulging of the cheeks and/or maxillary overgrowth (Figs 1 and 2) were graded as craniofacial deformity positive (CFD+). Those without or with unclear craniofacial deformities were graded as craniofacial deformity negative (CFD-). Some features of craniofacial deformities, such as depression of the bridge of the nose and mongoloid eye slant were excluded as they were considered as racial features (Kaw, 1993; McCurdy and Lam, 2005). Demographic, laboratory and clinical data were retrieved from patient folders.

After a two week interval, all photographs were re-evaluated by both examiners. Excellent agreement with a kappa value of 0.813 was achieved between the two evaluations.

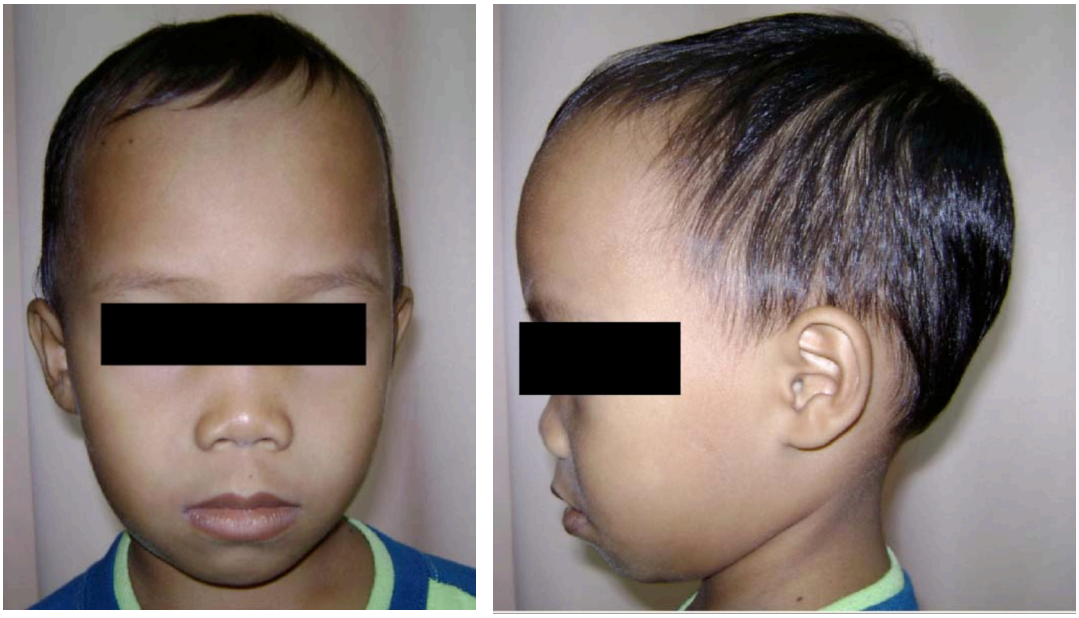

Fig 1–Thalassemia patient with frontal bossing.

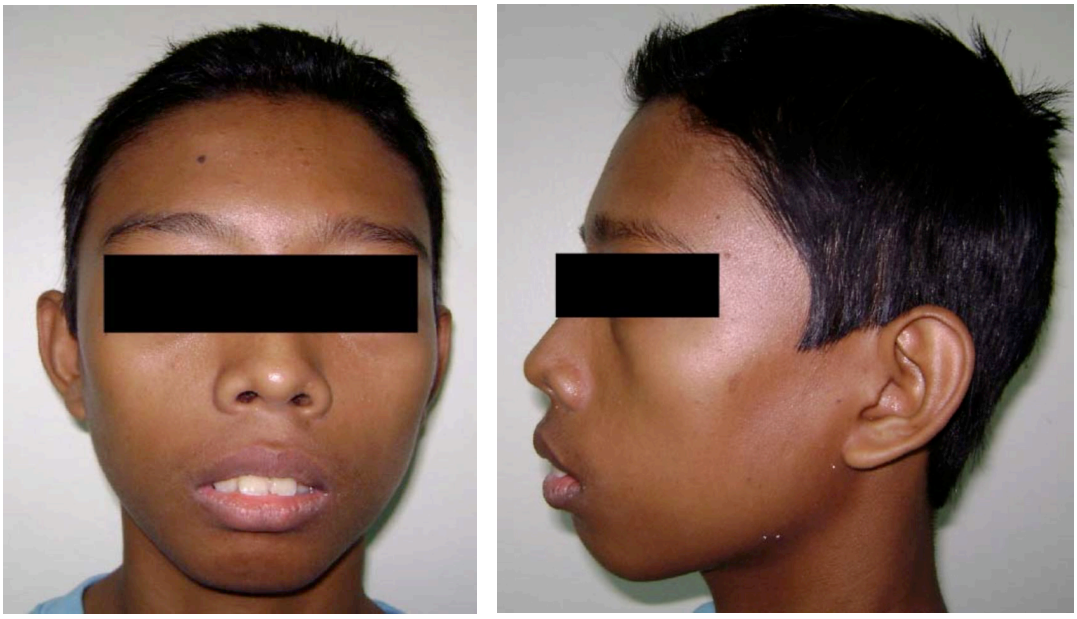

Fig 2–Thalassemia patient with obvious bulging of the cheeks, maxillary overgrowth and protrusion of maxillary teeth (chipmunk face).

The sample size for the prevalence of craniofacial deformity among TDT patients was calculated to give a precision of 0.14 with a 95% confidence interval. For numerical data comparisons between CFD+ and CFD- patients, mean and standard deviation were used if the data were normally distributed otherwise

median and interquartile range were used. Frequencies and percentages were used for categorical data. The independent *t*-test, Mann-Whitney test, chi-square test and Fisher exact test were used where applicable. The significance was defined as $p<0.05$. Data was entered into and analyzed using the Statistical Program for the Social Sciences, version 12.0.1.

The study was approved by the Research Ethics Committee (Human), Universiti Sains Malaysia, Number USMKK/PPP/JEPeM [198.4(2.2)].

RESULTS

During the 6 month study period, 52 patients were registered at the Pediatric Day Care Unit for regular blood transfusions. Forty-three patients (21 males and 22 females) who met inclusion criteria were enrolled in the study. The mean ±SD age of the patients was 11.6±4.8 years (range, 3.4-21.8 years). The majority of subjects (74.4%) had HbE/β thalassemia; 16.3% had β-thalassemia major and the rest had other types of thalassemia (β-thalassemia intermedia, HbH constant spring and HbH disease). Demographics of the patients in this study are shown in Table 1.

Nineteen out of 43 TDT patients (44.2%; confidence interval, 30.2-58.2%) had craniofacial deformities (CFD+). The comparison between the CFD+ and CFD- groups showed no significant differences in any of the clinical parameters (Table 2). The percentage of craniofacial deformities (CFD) was not significantly higher among males than females (11/21 (52.4%) *vs* 8/22 (36.4%), respectively; $p= 0.29$). Patients with different diseases did not have significant differences in craniofacial deformities [13/32 (40.6%) *vs* 6/11 (54.5%), respectively]; $p=0.50$).

Table 1
Demographics of patients enrolled in the study (N=43).

Characteristics	No. (%)
Sex	
Male	21 (48.8)
Female	22 (51.2)
Type of disease	
HbE/β thalassemia	32 (74.4)
Others	11 (25.6)
Frequency of transfusions	
2-4 weeks	32 (74.4)
>4 weeks	11 (25.6)
Chelation treatment	
No	14 (32.6)
Yes	29 (67.4)
Splenectomy	
No	31 (72.1)
Yes	12 (27.9)
Height[a]	
P<3rd	18 (47.4)
P 3rd-97th	20 (52.6)
Weight[a]	
P<3rd	20 (52.6)
P 3rd-97th	18 (47.4)

[a]P, percentile recorded for patients ≤ 18 years old (N=38).

The median± interquartile range (IQR) in age at the start of blood transfusions was not significantly younger in the CFD+ group than the CFD- group (3.0±2.5 years *vs* 3.4±3.3 years, respectively; $p=0.50$). Patients with regular blood transfusions (every 2-4 weeks) did not have a significantly lower prevalence of CFD than regularly transfused patients [13/32 (40.6%) *vs* 6/11 (54.5%), respectively; $p=0.50$]. The median ±IQR for pretransfusion hemoglobin levels was not significantly lower in the CFD+ group than in the CFD- group (63.0±10.3 g/l *vs* 67.0±7.4 g/l, respectively; $p=0.714$).

There were no significant differences between patients who did and did not

Table 2
Comparison between CFD+ and CFD- groups.

Variables	CFD-	CFD+	*p*-value
Age, median (IQR), years	11.6 (6.7)	11.5 (9.08)	0.608
Sex			
Male, No. (%)	10 (47.6)	11 (52.4)	0.290
Female, No. (%)	14 (63.6)	8 (36.4)	
Type of disease			
HbE/β thalassemia, No. (%)	19 (59.4)	13 (40.6)	0.495
Others, No. (%)	5 (45.5)	6 (54.5)	
Age at diagnosis, median (IQR), years	1.7 (3.4)	1.7 (1.2)	0.943
Age at start of transfusion, median (IQR), years	3.4 (3.3)	3.0 (2.5)	0.501
Frequency of transfusion			
Every 2-4 weeks, No. (%)	19 (59.4)	13 (40.6)	0.495
Greater than 4 weeks, No. (%)	5 (45.5)	6 (54.5)	
Hb level at diagnosis, mean (SD), g/l	61.0 (10.0)	61.0 (22.4)	0.941
Median pretransfusion Hb, median (IQR), g/l	67.0 (7.4)	63.0 (10.3)	0.714
Chelation treatment			
No, No. (%)	7 (50.0)	7 (50.0)	0.594
Yes, No. (%)	17 (58.6)	12 (41.4)	
Median serum ferritin, median (IQR), pmol/l	6,909.1 (4,554.1)	5,346.3 (7,030.5)	0.746
Splenectomy			
No, No. (%)	18 (58.1)	13 (41.9)	0.633
Yes, No. (%)	6 (50.0)	6 (50.0)	
Age at splenectomy, median (SD), years	10.6 (6.8)	6.8 (6.8)	0.361
Height			
P<3rd, No. (%)	11 (61.1)	7 (38.9)	0.944
P 3rd-97th, No. (%)	12 (60.0)	8 (40.0)	
Weight			
P<3rd, No. (%)	13 (65.0)	7 (35.0)	0.552
P 3rd-97th, No. (%)	10 (55.6)	8 (44.4)	

SD, standard deviation; IQR, interquartile range; P, percentile recorded for patients ≤ 18 years old. Significance set at $p<0.05$.

receive chelation therapy [17/29 (58.6%) CFD- *vs* 12/29 (41.4%) CFD+; $p=0.59$]. Median serum ferritin levels were not-significantly higher in CFD- than CFD+ patients ($p=0.71$). Both groups had the same number of patients who underwent splenectomy. Patients in the CFD+ group had a nonsignificant difference in age of splenectomy compared to the CFD- group (median ±IQR= 6.8± 6.8 years *vs* 10.6± 6.8 years, respectively; $p=0.361$).

Regarding developmental status, 11 out of 18 patients (61.1%) who were under the third percentile for height were CFD- and 7 out of 18 patients (38.9%) were CFD+. Sixty-five percent of patients under the third percentile for weight were CFD- and 35% were CFD+.

DISCUSSION

Two previous studies by Logothetis *et al* (1971) and Abu Alhaija *et al* (2002) identified the prevalence and graded the severity of CFD among β-thalassemia major patients. The former evaluated CFD among Greek patients aged 2 to 28 years and the latter evaluated CFD among Jordanian children aged 6 to 15 years. Both studies showed similar results: 31.9-33% had a normal appearance, 26-33.3% had grade 1 CFD; 20.3-24% had grade 2 CFD and 14.4-17% had grade 3 CFD. Both reports graded CFD into four grades: grade 0, no CFD; grade 1, slight depression of the nose, puffiness of the eyelids and no apparent maxillary overgrowth [mild mongoloid appearance, (Logothetis *et al*, 1971)]; grade 2, mild maxillary overgrowth and slight bulging of the cheeks and frontal bones; grade 3, prominent overgrowth of the maxilla, frontal and cheekbones, distinct depression of the nose and protrusion of anterior teeth (chipmunk faces).

In our study, the prevalence of CFD among TDT patients was 44.2%. Applying our classification of CFD (CFD- was grade 0 or 1 while CFD+ was grade 2 or 3) to the studies by Logothetis *et al* (1971) and Abu Alhaija *et al* (2002) showed the prevalences of CFD were 34.8% and 41%, respectively, lower than our results. However, their studies graded only β-thalassemia major patients whereas in our study, HbE/β thalassemia patients constituted the majority (74.4%) of patients, while β-thalassemia major patients constituded only a small minority (16.3%) of patients. A subanalysis of our study showed a non-significantly higher prevalence of CFD among β-thalassemia major patients (57.1%) than among HbE/β thalassemia patients (40.6%) which suggests a possible role of disease severity on development of CFD.

Before 2006, chelating agents were not freely accessible for thalassemia patients in Malaysia. Our thalassemia patients received less than optimum treatment with a late start in blood transfusions and low hematocrit transfusion regimen to avoid iron overload. This regimen is known to expose patients to anemia-related complications, including CFD (Mohamed and Jackson, 1998; Taher *et al*, 2006).

Reports about surgical correction of thalassemia-induced CFD have included many thalassemia intermedia cases with striking dentofacial deformities (Drew and Sachs, 1997; Mortazavi and Khojasteh, 2007). These reports have highlighted the role of suboptimal treatment of intermediate thalassemia patients in the development of CFD which has a negative social and psychological impact on these patients. Our group of TDT patients did have patients severe disfigurement requiring surgical correction.

An association between development of CFD among thalassemia patients and their treatment has been reported in previous studies. Logothetis *et al* (1971) reported CFD among β-thalassemia major patients correlated positively with age and duration of symptoms. They also found more severe CFD were present in patients with lower hemoglobin levels. Abu Alhaija *et al* (2002) found CFD among β-thalassemia major patients increased with age and duration of symptoms. Karagiorga-Lagana *et al* (1987) found maintenance of the mean pretransfusion hemoglobin level at 10 g/dl, resulted in an improvement in CFD among thalassemia intermedia patients over a period of 6 to 18 months. Our study showed no significant associations between clinical parameters and CFD (Table 1).

In our study, boys had a nonsig-

nificantly greater chance of having CFD (52.4%) than females (36.4%). Pusaksrikit *et al* (1987), found skeletal class 2 (prominent maxilla) CFD in severe thalassemia patients were more prominent in boys than girls. This suggests a more active marrow and a larger skeleton are present in boys.

In our study, patients with HbE/β thalassemia had a nonsignificantly lower prevalence of CFD (40.6%) than other types of thalassemia (54.5%), which could be attributed to milder anemia in the former group. The CFD+ group started their blood transfusion not significantly earlier (3.0 ± 2.50 years) than the CFD- group (3.4 ± 3.31 years). This may indicate a slightly worse anemia in the CFD+ group. Those who received 2-4 weekly blood transfusions a nonsignificantly lower percentage of CFD (40.6%) than those of received less regular blood transfusions (54.5%). Although, the mean hemoglobin levels at diagnosis were similar between the two groups, the mean pretransfusion hemoglobin level was nonsignificantly lower in the CFD+ group. The above findings may support the importance of regular blood transfusions to reduce CFD.

Patients with CFD required a nonsignificantly earlier splenectomy, which may indicate earlier clinical symptoms in this group. Logothetis *et al* (1971) suggested early transfusion and early splenectomy may help to minimize CFD among β-thalassemia major patients. Early transfusion and early splenectomy in β-thalassemia major patients are signs of efficient treatment. In thalassemia intermedia patients, this may reflect severity of disease. However, early splenectomy is no longer recommended due to considerable health risks (Cadili and de Gara, 2008). From 2006 onwards, we are expecting an improvement in the clinical manifestations of TDT patients in Malaysia due to financial support from the Malaysian government for the control and management of thalassemia.

This is the first report of CFD among Malay TDT patients. With the current treatment regimen, CFD are still prevalent. No significant association was seen with the clinical data. CFD were nonsignificantly more prevalent among patients with severe disease and less efficient treatment. Larger studies with greater sample sizes are needed to assess these results.

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REFERENCES

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.

Bassimitci S, Yucel-Eroglu E, Akalar M. Effects of thalassaemia major on components of the craniofacial complex. *Br J Orthod* 1996; 23: 157-62.

Cadili A, de Gara C. Complications of splenectomy. *Am J Med* 2008; 121: 371-5.

Cannell H. The development of oral and facial signs in beta-thalassaemia major. *Br Dent J* 1988; 164: 50-1.

Chan YL, Pang LM, Chik K W, Cheng JC, Li CK. Patterns of bone diseases in transfusion-dependent homozygous thalassaemia major: predominance of osteoporosis and desferrioxamine-induced bone dysplasia. *Pediatr Radiol* 2002; 32: 492-7.

Drew SJ, Sachs SA. Management of the thalas-

semia-induced skeletal facial deformity: case reports and review of the literature. *J Oral Maxillofac Surg* 1997; 55: 1331-9.

Jackson IT, WeelF, Crookendale WA, McMichan J. Gross jaw deformities in thalassaemia major. *Eur J Plastic Surg* 1987; 10: 32-6.

Karagiorga-Lagana M, Voskaki E, Sbyrakis S, Karaklis A. Blood transfusions for the prevention of bone deformities in thalassemia intermedia. *Birth Defects Orig Artic Ser* 1987; 23: 435-9.

Kaw E. Medicalization of racial features: Asian American women and cosmetic surgery. *Med Anthropol Q* 1993; 7: 74-89.

Logothetis J, Economidou J, Constantoulakis M, Augoustaki O, Loewenson RB, Bilek M. Cephalofacial deformities in thalassemia major (Cooley's anemia). A correlative study among 138 cases. *Am J Dis Child* 1971; 121: 300-6.

Malaysian Health Technology Assessment. Management of transfusion dependent thalassaemia. Kuala Lumpur: Ministry of Health, 2009. [Cited 2009 Nov 14]. Available from: URL: http://www.moh.gov.my

McCurdy JA, Lam SM. Cosmetic surgery of the Asian face. New York: Thieme, 2005.

Mohamed N, Jackson N. Severe thalassaemia intermedia: clinical problems in the absence of hypertransfusion. *Blood Rev* 1998; 12: 163-70.

Mortazavi SH, Khojasteh A. Superior repositioning of the maxilla in thalassemia-induced facial deformity: report of 3 cases and a review of the literature. *J Oral Maxillofac Surg* 2007; 65: 1023-31.

Orzincolo C, Castaldi G, Bariani L, Scutellari P N. The evolutionary effects of therapy on the skeletal lesions in beta-thalassemia. *Radiol Med* 1994; 87: 381-8.

Phadke SR, Agarwal S. Phenotype score to grade the severity of thalassemia intermedia. *Indian J Pediatr* 2003; 70: 477-81.

Pusaksrikit S, Hathirat P, Isarangkura P, Cephalometric radiography in thalassemic patients. *Birth Defects Orig Artic Ser* 1987; 23: 421-7.

Sripichai O, Makarasara W, Munkongdee T, *et al*. A scoring system for the classification of beta-thalassemia/Hb E disease severity. *Am J Hematol* 2008; 83: 482-84.

Taher A, Isma'eel H, Cappellini MD. Thalassemia intermedia: revisited. *Blood Cells Mol Dis* 2006; 37: 12-20.

Weatherall DJ, Clegg JB. The thalassaemia syndromes. Oxford: Blackwell Science, 2001.