SHORT STATURE AND TRUNCAL SHORTENING IN TRANSFUSION DEPENDENT THALASSEMIA PATIENTS: RESULTS FROM A THALASSEMIA CENTER IN MALAYSIA

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Abstract. One of the major complications in patients with transfusion dependent thalassemia is growth impairment secondary to iron overload. We studied the growth status in 66 patients with beta-thalassemia major and HbE-beta thalassemia who were transfusion dependent, aged from 2 to 24 years, and 66 controls matched for sex and age. The prevalence of short stature in transfusion-dependent thalassemics was 54.5% compared to 4.5% in control group ($p<0.001$). Short stature was more prevalent in those above the age of 10 years in this study group (83.3% *vs* 16.7%). Transfusion dependent thalassemics with short stature were found to have significantly lower mean standing height standard deviation scores (SDS), sitting height SDS and subischial leg length SDS values ($p<0.001$). There was also a significant difference between the mean sitting height SDS and the mean subischial leg length SDS in our thalassemics with short stature, suggesting that the short stature was due to disproportionate truncal shortening. Serum ferritin levels were significantly higher in transfusion dependent thalassemics who were short compared to those who were of normal height ($p = 0.002$). However, the mean pre-transfusion hemoglobin levels did not differ significantly between patients with short stature and those with normal height ($p = 0.216$). The prevalence of short stature also did not differ significantly between those with beta-thalassemia major and those with HbE-beta thalassemia ($p = 0.32$). This study highlighted the importance of providing optimal treatment in these patients, including monitoring of growth parameters and optimizing iron chelation therapy.

INTRODUCTION

The thalassemias are a heterogenous group of inherited diseases whose implications encompass a broad spectrum of human health. The most important forms of thalassemia result from autosomal mutant genes that reduce the rate of synthesis of the alpha and beta polypeptide chains of HbA, designated alpha and beta thalassemia, respectively. A decrease in either alpha or beta chain synthesis has several deleterious effects on red cell production and survival and directly leads to the clinical phenotype observed in individual patients (Nathan and Oski, 1992). Three clinically separable forms of thalassemia exist, *ie* asymptomatic thalassemia minor, thalassemia intermedia and thalassemia major.

In Malaysia, both thalassemia major and HbE-beta thalassemia are becoming an important public health problem. There are currently about 2,400 transfusion dependent thalassemics in the country. Data on morbidity amongst our patients are lacking. With the introduction of regular transfusion and chelation therapy with desferrioxamine, increased lifespan and improved quality of life are now possible for these patients (Olivieri and Brittenham, 1997). Despite this approach, a significant proportion of the children continue to have problems with growth and puberty (Kwan *et al*, 1995). The cause of short stature is multi-factorial but is mainly due to iron overload. Other contributing factors include suboptimal blood transfu-

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sion, desferrioxamine toxicity (Olivieri *et al*, 1995), delayed puberty or abnormalities of the thyroid and growth hormone (GH)-insulin like growth-factor (IGF-I) axis (Low, 1997).

Maintenance of a pre-transfusion hemoglobin level around 9.5g/dl has been shown to result in improved control of body iron burden and impaired growth (Cazzola *et al*, 1995). Serum ferritin level has been reported to have a direct relationship to the degree of growth retardation or reduction in height velocity amongst the thalassemics (Kattamis *et al*, 1990).

The aims of this study were to investigate the problem of short stature amongst our transfusion dependent thalassemics and the associated factors that might contribute to the growth impairment. We report here the results of our study of growth and body proportion on 66 transfusion dependent thalassemics attending the thalassemia clinic at the Hospital Universiti Kebangsaan Malaysia (HUKM), Kuala Lumpur, Malaysia.

MATERIALS AND METHODS

A case-control study was conducted between June 1999 and December 1999 on 66 children with beta thalassemia major and HbE-beta thalassemia, aged between 2 and 24 years, who were receiving regular blood transfusions (2 to 8 weekly) at Universiti Kebangsan Malaysia Hospital. Data on socio-demographic, type of thalassemia, frequency of blood transfusion, numbers of blood transfusion received in the past 12 months, pre-transfusion hemoglobin level in the past 12 months, the mean hemoglobin level, and the mean serum ferritin level were recorded. Sixty-six healthy children matched for age group, sex and ethnicity were used as controls. Informed consent for anthropometric measurement was obtained from patients and controls, or their parents.

The auxological data (standing height and sitting height) were obtained using a wall-mounted Harpenden stadiometer. Measurements were taken by a single observer (AH). For each measurement, the mean value from three readings was taken. The subischial leg length measurement was determined by subtracting the sitting height from the standing height. Reference data from Tanner and Whitehouse, for cross-sectional-type standards for height attained and individual-type (longitudinal) standards for sitting height and subischial leg length (boys and girls) were used (Tanner *et al*, 1966). The height, sitting height and subischial leg length standard deviation scores of 36 thalassemics with short stature were compared with those obtained from 36 age- and sex-matched controls. The data was summarised and analysed by using SPSS (version 9.0) statistical software. Chi-square and Student's *t*-test were used to analyse the data. The results were expressed as the mean and standard deviation. A p-value of <0.05 was taken as significant.

RESULTS

Table 1 shows the socio-demographic and clinical characteristics of the patients and controls. There were 36 (54.5%) male and 30 (45.5%) female patients. Thirty-one (47%) were Malays and 35 (53%) were Chinese. Patients with beta thalassemia major comprised 80.3% of the total transfusion dependent thalassemics, whilst the rest were HbE-beta thalassemia patients. Seventy-five percent of the patients were above ten years old.

The prevalence of short stature amongst the transfusion dependent thalassemics was 54.5% and 4.5% in the control group (Table 2A). Short stature was more prevalent in those above 10 years old (83.3%) compared to those below 10 years old (16.7%) (data not shown). There was no significant difference found in the prevalence between the male and female patients (50% *vs* 60%) (data not shown).

There was no significant difference found in the prevalence of short stature between the patients with beta thalassemia major and HbE-beta thalassemia (Table 2B). A significant difference was noted between the mean sitting height SDS and mean subischial leg length SDS in the thalassemics with short stature (Table

Table 1
Socio-demographic and clinical characteristics of children with transfusion dependent thalassemia and controls.

	Thalassemia (n = 66)	Controls (n = 66)	p-value
Sex			
Male	36 (54.5)	34 (51.5)	0.727
Female	30 (45.5)	32 (48.5)	
Race			
Malay	31 (47)	33 (50)	0.728
Chinese	35 (53)	33 (50)	
Age group (years)			
0-4	6 (9.1)	6 (9.1)	
5-9	11 (16.7)	11 (16.7)	NA[b]
10-14	19 (28.8)	19 (28.8)	
15-19	21 (31.8)	21 (31.8)	
>19	9 (13.6)	9 (13.6)	
Diagnosis			
beta thalassemia major	53 (80.3)	-	
HbE-beta thalassemia	13 (19.7)	-	
Transfusion interval (weeks)			
2-4	28 (42.4)		
4-6	32 (48.5)		
6-8	6 (9.1)		

[a]Figures in parentheses indicate percentages unless indicated otherwise.
[v]NA = Not applicable.

Table 2A
Number of transfusion dependent thalassemics and controls with standing height less than the third percentile (Tanner and Whitehouse, 1965).

	No. of patients with standing height < 3rd percentile (%)	p-value
Thalassemics (n = 66)	36 (54.5%)	<0.001
Controls (n = 66)	3 (4.5%)	

Table 2B
Number of patients with standing height less than third percentile according to the type of thalassemia.

	No. of patients < 3rd percentile (%)	p-value
Beta thalassemia major (n = 53)	28 (52.8%)	0.32
HbE-beta thalassemia (n = 13)	8 (61.5%)	

Table 3
Mean values of standing height SDS, sitting height SDS, and subischial leg length SDS in 36 thalassemics with short stature versus 36 controls matched for age and sex.

	Thalassemics (n = 36)	Controls (n = 36)	p-value
Mean standing height SDS (SD)	-3.00 (0.89)	-0.78 (0.73)	<0.001
Mean sitting height SDS (SD)	-3.94 (1.18)	-1.29 (0.96)	<0.001
Mean subischial leg length SDS (SD)	-1.77 (0.92)	-0.09 (0.85)	<0.001

Table 4
Mean serum ferritin levels and pretransfusion hemoglobin levels in transfusion dependent thalassemics who are below and above the third percentile in height.

	Thalassemics with height < 3rd percentile (n = 36)	Thalassemics with height > 3rd percentile (n = 30)	p-value
Mean serum ferritin level (ng/ml) (SD)	7,991.86 (4,425.75)	5,078.73 (2,646.10)	0.002
Mean pretransfusion hemoglobin level (g/dl) (SD)	7.73 (0.99)	8.01 (0.76)	0.216

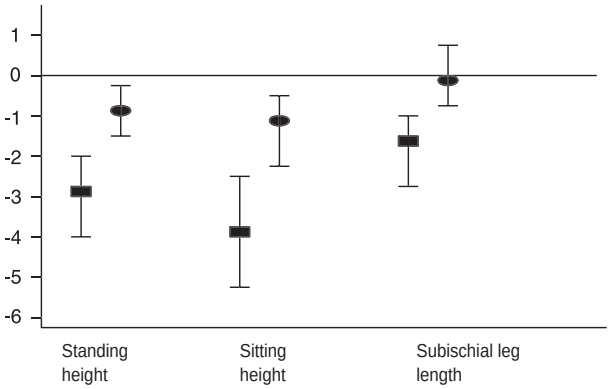

Fig 1-Graphs comparing standing height, sitting height and subischial leg length standard deviation scores (SDS) between ■, thalassaemics with short stature, with ●, age and sex matched controls. Values shown are mean ± SD. ($p<0.001$ for all 3 parameters).

3). The marked difference in the mean sitting height SDS (SD) between the thalassemics and the controls is shown in Fig 1.

Table 4 shows the comparison of the mean serum ferritin levels and the mean pre-transfusion hemoglobin levels in those who were less than third percentile versus those who were above third percentile in height.

DISCUSSION

The current published data have shown that the prevalence and degree of growth retardation amongst patients with thalassemia varies in different series. This is to be expected since there is wide heterogeneity in the clinical and hematological phenotypes of these patients, as well as in their treatment schedules and compliance (Kattamis *et al*, 1990). Our study showed that the prevalence of short stature amongst our transfusion dependent thalassemics was 54.5%. This prevalence is higher compared to the prevalence amongst Greek patients (35.3%) and also amongst Italian patients, aged 10-25 years old (37%) (Kattamis *et al*, 1990). The higher prevalence in our patients could be attributed to suboptimal chelation therapy since the use of the desferrioxamine is limited to patients who can afford it. In addition, compliance is a major problem in many patients who are on chelation therapy. The problem of instituting opti-

mal iron chelation amongst our patients was evident from our study which showed that the mean serum ferritin levels were worryingly high in both patients who were short and those of normal height.

It is also interesting to note that about 75% of the patients in our study are above 10 years old, which is the crucial age in relation to growth especially for the growth spurt occurring during puberty. In our study, short stature was more prevalent in those above 10 years old compared to those below 10 years old (83.3% *vs* 16.7%). It is likely that growth impairment in thalassemics commences at an earlier age, however further deceleration of growth probably takes place in the second decade (Kattamis *et al*, 1990). The next logical step would be to perform a prospective study to monitor the growth of these thalassemics and pinpoint the age or the age range whereby growth actually decelerates.

We found no difference in the prevalence of short stature between those with HbE-beta thalassemia and those with thalassemia major. This is an important finding since the majority of patients with HbE-beta thalassemia have the thalassemia intermedia phenotype, hence the local transfusion policy for these patients has been to transfuse only when the hemoglobin drops below 7g/dl or if they are symptomatic. Our results suggested that this transfusion approach might have been detrimental to their growth as evidenced by the high prevalence of short stature. We however only included patients with HbE-beta thalassemia who were transfusion-dependent. A bigger study is warranted to address this issue further.

Thalassemics with suboptimal mean pre-transfusion hemoglobin levels are expected to be at a higher risk of growth impairment. Although our study showed that those who were short had lower mean pre-transfusion hemoglobin levels compared to those with normal height, the difference was not statistically significant. The hypertransfusion policy was only strictly applied in our unit in the recent years. Even then, the inadequate volume of blood supplied and transfused means that the aim of maintaining a pre-transfusion hemoglobin of 9.5-10.5g/dl was often not achieved in patients with thalassemia major. Hence, there is a possibility that patients who had short stature might have had even lower levels of pre-transfusion hemoglobin prior to the study period. Our data also suggested that the failure to maintain an optimal hemoglobin level is only one of the factors contributing to the impairment of growth of the patients with thalassemia.

The correlation based on the use of desferrioxamine was not performed as very few of the 66 patients were on optimal desferrioxamine treatment, *ie* 30-50mg/kg/day for 5 nights a week. Furthermore a significant proportion of them started using desferrioxamine since less than 5 years ago. We instead used the mean serum ferritin levels and found that the levels were higher in patients who were short. This concurred with data from other studies on the relationship between serum ferritin levels and growth retardation (Kattamis *et al*, 1990; Modell and Berdoukas, 1981). However, serum ferritin is not the ideal parameter to assess iron overload. The goal standard for body iron status is liver iron content, which could not be done in our center.

We also attempted to investigate for the presence of disproportionate shortening in our thalassemics who were short. We found that there were significant differences between the standing height SDS, sitting height SDS and subischial leg length SDS of the patients when compared to the controls. More importantly, the mean sitting height SDS and the mean subischial leg length SDS in thalassemics with short stature were also found to be significantly different. This suggested that our patients who were short had evidence of disproportionate truncal shortening. Our findings concurred with that found by Rodda *et al*, in which disproportionate truncal shortening were detected in thalassemics who were short (Rodda *et al*, 1995). The iron overload that was found in our patients could be one of the factors that contributed to the disproportionate truncal shortening. Other contributory factors such as pubertal delay and desferrioxamine toxicity need to

be ruled out as possible causes in future studies. However, the likelihood of desferrioxamine toxicity was minimal since the majority, if not all, of our patients were actually under-chelated.

In conclusion, our study showed that there was a high prevalence of short stature amongst our transfusion dependent thalassemics. No significant difference was found between beta thalassemia major and HbE–beta thalassemia in terms of the prevalence of short stature. We also confirmed the presence of disproportionate truncal shortening in our thalassemics who had short stature. Higher serum ferritin levels contributed to the higher prevalence of short stature in our patients. This study also highlighted the importance of monitoring growth parameters amongst the thalassemics. Optimal management including optimal iron chelation treatment, optimal blood transfusion and monitoring of complications of iron overload remain the mainstays of treatment in these patients.

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