GROWTH VELOCITY IN TRANSFUSION DEPENDENT PREPUBERTAL THALASSEMIA PATIENTS: RESULTS FROM A THALASSEMIA CENTER IN MALAYSIA

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Abstract. Growth impairment is commonly seen in children with thalassemia despite regular blood transfusions and desferrioxamine treatments. We investigated the growth velocity of 26 prepubertal patients with beta-thalassemia or HbE-beta thalassemia who were transfusion dependent aged between 2 and 13 years. The prevalence of impaired growth velocity (*ie,* growth velocity less than the third percentile) amongst the transfusion dependent prepubertal thalassemics was 57.7% compared to 19.2% in the control group. The mean height velocity of the thalassemics was 11.1% less than controls but this difference was not statistically significant (4.23cm/year *vs* 4.76cm/year, p=0.08). The mean serum ferritin level of the thalassemics with a height < 3rd percentile was higher compared to those with a height > 3rd percentile (4,567.0 *vs* 2,271.0, p=0.01). Our study showed that there was a high prevalence of impaired growth velocity amongst our transfusion dependent prepubertal thalassemics. This highlights the problem of inadequate chelation therapy, and compliance with chelation therapy amongst our patients. This study emphasizes the importance of monitoring growth parameters and optimal iron chelation therapy in these patients.

INTRODUCTION

Beta-thalassemia major and HbE-beta thalassemia are a common inherited hematological conditions in Southeast Asia. In Malaysia, it poses a significant public health problem with an estimated 2,400 transfusion dependent thalassemics in the country. Approximately 3% to 5% of the Malaysian population are heterozygous carriers of beta-thalassemia, and it is expected that 120 to 130 newborns are born with transfusion dependent beta-thalassemia each year (George *et al*, 1992). Despite medical advances, a significant proportion of these patients continue to have problems with growth and puberty (Masala *et al*, 1984; Kattamis *et al*, 1990; Theodorotis *et al*, 1998). The cause of growth impairment is multi-factorial and the precise pathogenesis has not yet been elucidated. Amongst the contributory factors are suboptimal blood transfusions, hematological variants, iron overload, desferrioxamine toxicity, delayed puberty or abnormalities of the thyroid and growth hormone (GH)-insulin like growth-factor (IGF-I) axis (Kattamis *et al*, 1990; Low 1997). Serum ferritin levels have been reported to have a direct relationship with the degree of growth retardation or reduction in height velocity amongst thalassemics (Kattamis *et al*, 1990).

The aims of this study were to investigate growth amongst prepubertal transfusion dependent thalassemics and the associated factors that might contribute to deceleration of growth velocity. We report here the results of our study of growth velocity on 26 patients

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MATERIALS AND METHODS

A case-control study was conducted between January 2004 and June 2005 on 26 prepubertal children with beta-thalassemia major or HbE-beta thalassemia, aged between 2 and 13 years, who were receiving regular blood transfusions at HUKM. A puberty stage less than two using the method of Tanner (1962) was taken as prepubertal. Children with other illnesses that could independently contribute to poor growth, such as renal, primary skeletal disorders and severe malnutrition were excluded from the study. None of the study subjects was on long-term medication known to affect growth. Data regarding socio-demographics, type of thalassemia, frequency of blood transfusions, number of blood transfusions received during the past 12 months, pre-transfusion hemoglobin levels in the past 12 months, the mean hemoglobin level, and the mean serum ferritin level were recorded. Twenty-six healthy children matched for age group, sex and ethnicity were used as controls. Informed consent for standing height measurements was obtained from patients and their parents.

The standing height measurements were obtained using a standard anthropometric technique with a wall-mounted Harpenden stadiometer. Measurements were taken by a single investigator (Arini MI). For each measurement, the mean value from three readings was taken. The height measurements were taken every 6 months for one year. Height velocity was calculated by determining the increment of height between the successive visits. Reference data from Tanner and Whitehouse, for cross-sectional-type standards for height attained and height velocity were used (Tanner *et al*, 1966). The standing height and height velocity of 26 prepubertal thalassemics were compared with those obtained from 26 age- and sex-matched controls. The data was summarized and analyzed using SPSS 11.0 statistical software. Chi-square and Student's *t*-test were used to analyze the data. The results were expressed as means and standard deviations. A p-value of less than 0.05 was taken as significant.

RESULTS

During the study period a total of 32 patients were eligible. Six patients were excluded from analysis of growth velocity because the respective controls were lost to follow-up. Therefore, 26 patients were evaluable for growth velocity assessment. Table 1 shows the characteristics of the patients and the controls. There were 14 (53.8%) male and 12 (46.2%) female patients. Twenty (76.9%) were Malay and 6 (23.1%) were Chinese. Patients with beta-thalassemia major and HbE-beta thalassemia each contributed to 50% of the total transfusion dependent thalassemics.

The prevalence of impaired growth velocity (*ie*, growth velocity less than the third percentile) amongst the transfusion dependent thalassemics was 57.7% compared to 19.2% in the control group (Table 2). The mean height velocity of the transfusion dependent thalassemics was 11.1% less than the controls, but this was not statistically significant (4.23 cm/year *vs* 4.76 cm/year, p=0.08). The mean height velocity was significantly different in the female subgroup compared to controls (3.85 cm/year *vs* 4.54 cm/year, p=0.03).

Table 3 shows the comparison of the mean height velocity, mean serum ferritin level, mean age, mean pre-transfusion hemoglobin, and mean number of transfusions per year in those who were less than the third percentile versus those who were above the third percentile in height velocity. All 32 patients who were eligible for this study were included in this analysis.

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

	Thalassemia (*n* = 26)	Controls (*n* = 26)	p-value
Sex			
Female	12 (46.2)	12 (46.2)	1.00
Male	14 (53.8)	14 (53.8)	
Race			
Malay	20 (76.9)	20 (76.9)	1.00
Chinese	6 (23.1)	6 (23.1)	
Mean age (years) (SD)	8.48 (2.68)	8.55 (2.52)	0.76
Diagnosis			
Beta-thalassemia major	13 (50)	NA[b]	
HbE-beta thalassemia	13 (50)		

[a]Figures in parentheses indicate percentages unless indicated otherwise.
[b]NA=not applicable, SD=standard deviation

Table 2
Number of transfusion dependent prepubertal thalassemics and controls with growth velocity less than the third percentile.

	No. of patients with growth velocity < 3rd percentile (%)	p-value
Thalassemics (*n*=26)	15 (57.7)	0.005
Controls (*n*=26)	5 (19.2)	

In addition, there was no significant difference found in the prevalence of impaired growth velocity between the patients with beta-thalassemia major and HbE-beta thalassemia. Also, there was no significant difference found in the mean height velocity between the thalassemia groups (3.89 cm/year *vs* 4.26 cm/year, p=0.45). However, the mean serum ferritin level was significantly higher in the patients with beta-thalassemia major compared to patients with HbE-beta thalassemia (5,392.0 *vs* 1,733, p<0.01). Also, the mean pre-transfusion hemoglobin level was significantly higher in the patients with beta-thalassemia major compared to patients with HbE-beta thalassemia (8.7 *vs* 7.0, p<0.01).

DISCUSSION

Our study showed that the prevalence of impaired growth velocity amongst our transfusion dependent prepubertal thalassemics was 57.7%. This prevalence is higher than the prevalence amongst Greek thalassemic patients age 7-8 years (8%) (Theodorotis *et al*, 1998). Studies on growth velocity amongst young thalassemics are limited in number. A previous study carried out in our unit showed that the prevalence of short stature amongst transfusion dependent thalassemics age 2-24 years was 54.5% (Hamidah *et al*, 2001). In the study, short stature was more prevalent in those above 10 years old compared to those below 10 years old (83.3% *vs* 16.7%). This suggests the maximal deceleration in growth occurs after 10 years of age. Our study findings suggest growth impairment in thalassemics commences at an earlier age, however further deceleration of growth may take place in the

Table 3
Comparison between transfusion dependent prepubertal thalassemics with height velocity below and above the third percentile.

	Height velocity < 3rd percentile (*n* = 18)	Height velocity > 3rd percentile (*n* = 14)	Mean difference (95% CI)	p-value
Mean age (years) (SD)	8.87 (2.64)	7.85 (2.48)	1.02 (-0.85 to 2.89)	0.27
Mean height velocity (cm/year) (SD)	3.44 (0.57)	4.88 (1.69)	-1.44 (-2.45 to -0.44)	<0.01
Mean serum ferritin level (ng/ml) (SD)	4,567.0 (3,637.0)	2,271.0 (1,804.0)	2,295.0 (274.0 to 4,317.0)	0.02
Mean pretransfusion hemoglobin level (g/dl) (SD)	7.99 (1.14)	7.73 (1.43)	0.26 (-0.66 to1.19)	0.57
Mean no. of transfusions per year (SD)	8.94 (3.92)	8.21 (4.35)	0.73 (-2.26 to 3.78)	0.62

CI=confidence interval, SD=standard deviation

second decade. The second decade of life is the critical period for growth especially during puberty. Previous studies have shown that as thalassemia patients approach puberty, a proportion of patients develop growth retardation and pubertal failure (Borgna-Pignatti *et al*, 1985; Kattamis *et al*, 1990). The pathogenesis of late impairment of growth and sexual maturation in transfused patients with thalassemia major is generally believed to be directly related to iron toxicity, especially of the endocrine glands (Kattamis and Kattamis, 1995). In this study, the high mean ferritin level (4,567 ng/ml) in our patients may indicate that inadequate chelation is the likely cause of impaired growth velocity. During this study period, the use of iron chelation therapy with desferrioxamine in our patients is limited to patients who can afford it. Only 16 of 21 patients with mean ferritin levels > 2,000 ng/ml were on iron chelation therapy and 2 of 11 patients with a mean ferritin level < 2,000 ng/ml were on iron chelation therapy. In addition, compliance is a major problem in many patients who are on chelation therapy. We found that patients with a mean height velocity < 3rd percentile had higher mean ferritin levels than patients with a mean height velocity > 3rd percentile. These data suggest that younger thalassemia patients, given proper chelation therapy from an early age, may show improvements in growth.

In this study, the growth of patients with HbE-beta thalassemia was suppressed similarly to patients with beta-thalassemia major, even though their mean serum ferritin levels were significantly lower. This finding suggested that other factors might have played important roles in contributing to the growth impairment in this group of patients. The lower mean pre-transfusion hemoglobin level compared to patients with beta-thalassemia major may be one of the contributing factors to growth impairment in this group of patients. Previous studies reported that growth was found to be closely related to pre-transfusion hemoglobin levels (Kattamis *et al*, 1990). Suboptimal mean pre-transfusion hemoglobin levels may increase the risk of growth impairment. It was suggested that maintaining a pre-transfusion

hemoglobin level between 9.5 and 10.5g/dl may encourage normal growth (Kattamis *et al*, 1970, 1990).

We would like to acknowledge that free desferrioxamine has recently become available to our transfusion dependent thalassemics who are complicated by iron overload, irrespective of the socioeconomic status of the patients. Therefore, we recommend provision of effective counseling and equipping readily accessible technical services to the patients and their families in order to ensure good compliance with iron chelation therapy. This may be a major challenge for health professionals involved in the care of these patients. The next logical step would be to perform a study to ascertain other contributing factors, such as decreased synthesis of IGF-1, which may be secondary to a disturbed GH-IGF-1 axis (Soliman *et al*, 1999; Masala *et al*, 2003) and/or under nutrition, which could cause a negative effect on the final height of these patients.

The study was limited by the fact that it consisted of a small number of patients, hence reducing the study power. The fact that 19% of normal children in this study had a growth velocity of less than 3rd percentile is somewhat surprising. However, there is a wide range of growth velocity in normal growing children roughly from 4 to 7 cm a year for children age 6 to 11 years, and variation occurs based on whether they are early or late maturers. Perhaps another possible way of matching controls would be by calculating mid-parental height. Nevertheless the use of local controls was the strength of this study as growth curves for children based on our local population are lacking.

In summary, our study showed that there was a high prevalence of impaired growth velocity amongst our transfusion dependent prepubertal thalassemics. This suggests that growth impairment commenced early in the prepubertal age in these patients. It highlights the problem of inadequate chelation therapy and compliance with chelation therapy amongst our patients. In addition, suboptimal mean pre-transfusion hemoglobin levels may contribute to growth impairment in these patients. The findings of our study highlight the importance of optimal blood transfusions and optimal chelation therapy in these patients.

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