MALNUTRITION AND GROWTH ABNORMALITIES IN CHILDREN WITH BETA THALASSEMIA MAJOR

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Abstract. Abnormal linear growth (stunting) is characteristic of children with beta thalassemia major and has been variably and inconsistently attributed to multiple different mechanisms. Despite the coexistence of beta thalassemia with deficits of several micronutrients, global undernutrition as a principle cause of growth abnormalities has not been adequately studied. We prospectively studied 115 nonsplenectomized children (6 months - 6 years, 54 males, 61 girls) with beta thalassemia major who has not previously received chelation therapy. Most children had abnormal weight-for-age (WAZ) and height-for-age (HAZ) Z scores, however female children had lower WAZ ($p < 0.0001$) and HAZ ($p < 0.02$) compared to males. Mild to moderate degrees of acute wasting was also usual, and two males and one female had severe wasting. Severe weight deficits were more prevalent in the youngest ($p < 0.01$) and severe stunting in the older ($p = 0.01$) children. Nearly all children were < 50th percentile for both weight-for-age and height-for-age, and the majority were < 5th percentile. Of note, children were also disproportionately distributed below the 50th percentile for weight-for-height. Pre-transfusion hemoglobin was variably associated with anthropometric measurements. We conclude that not only is linear growth failure pervasive in our population with beta thalassemia major, but varying degrees of wasting are also typical. Further, weight deficits occur at an early age and appear to precede deficits in linear growth. Abnormal growth is not due to chelation therapy and is inconsistently associated with the degree of anemia. These patterns of growth abnormalities indicate general malnutrition as an important cause of growth failure in children with beta thalassemia.

INTRODUCTION

The inherited disease beta thalassemia major is associated with impaired growth velocity generally beginning after 6-8 years which results in stunting and delayed or absent puberty (Kattamis *et al,* 1990; Constantoulakis *et al,* 1975). Investigations into the etiology of the growth abnormalities have most often been contradictory and controversial, and have variably implicated an abnormal hypothalamic-pituitary-gonadal axis function, impaired hepatic synthesis of somatomedin, the effects of cellular hypoxia due to anemia, adverse effects associated with desferrioxamine therapy, among others (Costin *et al,* 1979; Wolman, 1969; De Virgiliis *et al,* 1988; Saenger *et al,* 1980). It has also been established that children with thalassemia have multiple nutritional defects including biochemical and clinical evidence of zinc deficiency as manifested by delayed growth and sexual maturation (Prasad *et al,* 1965; Silprasert *et al,* 1988). In addition, folic acid and B_{12} deficiency have been documented in patients with thalassemia. Vitamin E deficiency as well as low retinol, carotenoids, and retional binding protein have also been observed (Weatherall and Clegg, 1981; Saraya *et al,* 1984; Rachmilewitz *et al,* 1976; Giardini *et al,* 1981; Katerelos *et al,* 1979). Despite the coexistence of beta thalassemia with deficits of several specific micronutrients, a unifying hypothesis of general chronic undernutrition as a principle cause of growth abnormalities has not been adequately studied. We would predict however, that if such a hypothesis is plausible, deficits in ponderal growth would exist in conjunction with deficits in linear growth. Further, if thalassemia-associated stunting is the result of chronic general undernutrition we would also expect certain children to manifest weight abnormalities at a relatively early age.

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MATERIALS AND METHODS

One hundred and fifteen non-splenectomized children (54 males, 61 females) with beta thalassemia major aged six months to 15 years were enrolled from the thalassemia specialty clinic at the

Maharaj Nokhon Chiang Mai Hospital, Chiang Mai, Thailand. Data were prospectively collected in a cross-sectional fashion over a period of six months. Children were measured to the nearest 0.1 kg with a Schonle digital scale and height was measured to the nearest 0.1 cm using a Harpenden anthropometer. Measurements were compared to the age-and sex-specific reference standards of the US National Center for Health Statistics (NCHS) data (Hamill *et al,* 1979). Percent of median equivalents of standard deviation units (Z scores) were determined and nutritional status categorized according to the system of Waterlow (Waterlow, 1977). In this scheme, the reference mean Z score is zero, and Z scores greater than -1 for height-for-age (HAZ) and weight-for-height (WHZ) are considered normal whereas values of -2 SD or lower are considered to represent moderate to severe malnutrition as correlates of the percentage deviations from median criteria of Waterlow (Waterlow, 1972; 1992). The same cut-offs were applied to weight-for-age Z score (WAZ) as an extrapolation of the Gomez criteria (Gomez *et al,* 1955). A descriptive interpretation of these anthropometric indices is shown inTable 1 (Seoane and Latham, 1971). Blood hemoglobin concentration was measured prior to transfusion at the same visit as the anthropometry by spectrophotometric analysis after conversion of hemoglobin to cyanmethemoglobin (International Committee for Standardization in Hematology, 1978).

Chi-square (χ^2) tests of independence were used to examine the distribution of indices of anthropometry among the male and female children. Group comparisons of continuous data were made by Students' *t*-test except for WHZ which was assessed by Mann-Whitney U test since WHZ data were not normally distributed. Spearman correlation coefficients (rank order) were used to investigate the association between pre-transfusion hemoglobin concentration and anthropometry. All data are presented as mean ±SD. Significance is defined as $p < 0.05$.

RESULTS

No significant differences existed between the male and female children in age, weight, height, body mass index, or hemoglobin level (Table 2). The mean WAZ was -2.0 ± 2 for males and -2.9 ± 1 for females ($p < 0.0001$). More female than male children were below -1.00 SD ($p < 0.03$), with 64% of males and 78% of females being moderately to severely underweight (< -2.00 SD) according to weight-for-age criteria (Table 3). The most severe weigth deficits (<-3.00 SD) were more common in female than male children ($p < 0.01$). Female children also had a lower mean HAZ compared to male children (-2.3 ± 2 and -3.3 ± 2, respectively, $p < 0.02$). Although a greater proportion of females than males were below -1 SD (95% versus 76%, $p < 0.05$), the gender difference was not significant in those with more profound stunting (HAZ < -2.00

Table 1
Growth abnormalities and malnutrition*.

Type of malnutrition	Height-for-age	Weight-for-age	Weight-for-height
Ongoing			
Acute (short duration)	Normal	Low	Low
Chronic (long duration)	Low	Low	Low
Past	Low	Low	Normal

*Modified from Ref 23

Table 2
Anthropometric measurements and hemoglobin values of children with beta thalassemia.

	Males (n = 54)	Females (n = 61)
Age (m)	58.7 ± 47.0	60.5 ± 49.0
Weight (kg)	13.4 ± 6.0	13.2 ± 7.0
Height (cm)	100.7 ± 17.0	103.0 ± 18.0
BMI (kg/m^2)	15.3 ± 2.0	15.1 ± 1.0
Hemoglobin (g/dl)	5.7 ± 2.3	5.2 ± 2.3

SD or < -3.0 SD). The mean weight-for-height Z score was -0.4 ± 1.5 for males and -0.8 ± 0.7 for females (p = 0.29). And while 44% of females and 30% of males had evidence of acute wasting (WHZ <-1 SD), the difference was not significant (p = 0.37).

Relative to the percentile curves of the NCHS, nearly all of the children were below the 50th percentile for both weight-for-age and height-for-age, and the majority were below the 5th percentile (Table 4). Of note, the children were also disproportionately distributed below the 50th percentile for weight-for-height (82% of both males and females) although fewer were below the 5th percentile.

The interaction between age and nutritional status was also examined (Tables 5, 6, and 7). No association was detected between age and WHZ, however WAZ was significantly associated with age (p < 0.005) with severe weight dificits of <-2

Table 3
Percentage distribution of Z scores for weitht for age, height for age, and weight for height (54 males, 61 females).

Z score	Weight-for-age*		Height-for-age*		Weght-for-height**	
	Males	Females	Males	Females	Males	Females
> -1	21	6	24	5	70	56
≤ -1 to -1.9	15	16	21	17	22	41
≤ -2 to -2.9	43	34	18	22	8	3
≤ -3	21	44	37	56	-	-

* Difference between groups significant (see text for details)
** Difference between groups not significant

Table 4
Percent of children below the 5th and 50th percentile of weight-for-age, height-for-age, and weight-for-height (54 males, 61 females).

Percentile	Weight-for-age		Height-for-age		Weght-for-height	
	Males	Females	Males	Females	Males	Females
< 50th	90	100	91	100	82	82
< 5th	71	84	62	88	11	9

Table 5

Percentage distribution of height-for-age by age of children (54 males, 61 females).

HAZ*	Year of age				
	0-3	3-6	6-9	9-12	>12
> -1	4	9	-	-	-
≤ -1 to -1.99	1	7	8	-	3
≤ -2 to -2.99	-	8	7	3	3
≤ -3 to -3.99	3	7	7	1	4
≤ -4	-	5	3	12	5

* HAZ, Height-for-age Z score

Table 6

Percentage distribution of weight-for-age by age of children (54 males, 61 females).

WAZ*	Year of age 0-3	3-6	6-9	9-12	>12
> -1	5	6	2	-	-
≤ -1 to -1.99	2	5	4	1	3
≤ -2 to -2.99	14	8	9	4	2
≤ -3 to -3.99	11	2	2	5	2
≤ -4	8	3	-	-	2

* WAZ, Weight-for-age Z score

Table 7

Percentage distribution of weight-for-height by age of children (54 males, 61 females).

WHZ*	Year of age 0-3	3-6	6-9	9-12
> -1	7	26	21	8
≤ -1 to -1.99	2	16	8	7
≤ -2	3	2	-	-

* WHZ, Weight-for-height Z score

SD and < -3 SD more common in children younger than three years compared to those older than three years of age ($p < 0.01$). HAZ was also associated with age ($p < 0.02$), however the relationship was inverse with stunting being more profound in children older than six years of age compared to younger children ($p = 0.01$).

The pre-transfusion hemoglobin concentration was significantly correlated with HAZ in males but not females ($r = 0.33$, $p < 0.05$). Hemoglobin was significantly associated with WAZ in females but not males ($r = 0.26$, $p < 0.05$). Neither male or female WHZ correlated with the degree of anemia.

DISCUSSION

Growth failure as defined by short stature and abnormal height velocity is pervasive in children with beta thalassemia major. Evidence of growth retardation can occur as early as the first and second year of life in children with severe disease, although abnormalities most commonly do not become apparent until after age 6 to 8 years (Kattamis *et al,* 1990; Constantoulakis *et al,* 1975). The growth pattern of the children in our study is consistent with this observation, however the onset of height deficits was evident at a younger age and in a greater proportion of our population than expected. Further, these abnormalities in our group of children were not due to chelation therapy and were inconsistently associated with pre-transfusion hemoglobin levels. Abnormal height became more prevalent and was more severe in the children with advancing age. The advent of height deficits at an early age together with the association of prevalence and severity with advancing age are consistent with the hypothesis that chronic undernutrition has a central role in the etiology of the growth failure associated with thalassemia. It is of some interest that the female children had a higher prevalence of HAZ and WAZ deficits than the male children, although there was no difference in the severity of stunting nor was there a gender difference in weitht-for-height. Within this context we suspect that the observed gender differences were due to random error, specifically a Type II error.

While abnormalities of weight associated with thalassemia major have been previously noted, earlier reports have not generally provided information regarding the specific relationship of weight deficits to height, and have therefore not detailed the extent of wasting as a problem in beta thalassemia. In our study children, mild to moderate deficits in weight-for-height were common and the distribution of weight-for-height was disproportionately below the median. Further, abnormalities of weight-for-age were most frequent and pronounced in the children less than three years of age, an indication that acute malnutrition or wasting has its onset quite early in life in these children. We believe these observations provide convincing evidence of coexistent general malnutrition as a significant and common complication of childhood beta thalassemia. In this regard, the malnutrition of thalassemia major is reminiscent of the secondary malnutrition associated with many other primary disease states (Fuchs, 1990). It should be emphasized that due to the potentially large weight of the liver and spleen with advancing disease, both the prevalence and degree of malnutrition is most certainly greater than indicated by our use of weight measurements as the sole indicator of wasting. Based on our results, therefore, varying degrees of wasting appear to be typical in children with beta thalassemia. It is likely relevant that certain of the endocrine abnormalities associated with growth failure in children with beta thalassemia and delayed or absent puberty are similar or the same as those observed in primary protein energy malnutrition (Tenore and Vargas, 1993). We conclude therefore, that the anthropometric abnormalities in children with beta thalassemia indicate a primary role for undernutrition in the etiology of stunting associated with this disease. The type of anthropometric abnormalilites and the age-associations of the specific abnormalities are indistinguishable from those observed in the stunting due to primary malnutrition, that is the onset of acute malnutrition that evolves into chronic malnutrition and ultimately stunted growth. Futhure investigations should focus on further definition of the nutritional status of children with beta thalassemia as well as the potential relationship of coexistent secondary malnutrition to many of the other complications of this disease.

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