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Iron overload in beta thalassemia major patients

Atthanayaka Mudiyanselage Dilhara Sewwandi Karunaratna, JG Shirani Ranasingha, Rasnayaka Mudiyanselage Mudiyanse

ABSTRACT

Aims: Beta thalassemia is the most common monogenic hereditary hemoglobin disorder, which poses a major health burden to Sri-Lanka. Regular transfusions of erythrocytes required for survival of these patients lead to inevitable iron overload, which is manifested, by elevated serum ferritin levels. Progressive deposition of iron leads to dysfunction and failure of the major organs. The aim of this study was to evaluate the iron overload of the beta thalassemia major patients in one of the thalassemia centres in Sri Lanka and to find its effect on growth status of the patients. Methods: The study included forty patients with confirmed diagnosis of beta thalassemia major, undergoing any chelation treatment. The mean age of the study group was 10.97±5.9 years with a range of 2–20 years. The patients were interviewed for the socio-demographic variables and their medical histories were obtained from the hospital files. Serum ferritin concentration, height and weight of the patients were measured and body mass index (BMI) was calculated. Results: The mean serum ferritin concentration was 2992.2±1575.35 ng/ml which showed a significant correlation with age and duration of blood transfusion. The mean z-score for height was -2.3±1.06 and 50% of the patients were stunted. The mean z-score for BMI was -1.32±1.28 and 35% of the patients were wasted. Both height and BMI had no significant correlation with iron overload of the patients. Conclusion: Iron overload and growth retardation were common in beta thalassemia major patients of the treatment center evaluated in this study in Sri Lanka. However, there was no significant relationship between physical growth and iron overload.

Keywords: Beta thalassemia major, Growth status, Iron overload

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INTRODUCTION

Beta thalassemia is the most common monogenic hereditary hemoglobin disorder, which poses a major health burden in Sri Lanka. The national incidence of 60–80 cases per year together with the estimated life span

of 20–25 years has resulted in a patient load exceeding 1500 patients. The highest prevalence of beta thalassemia major disease is seen in three provinces namely Wayamba, North Central and Uva. However, cases are found all over the country. The prevalence of beta thalassemia trait among Sri Lankan population varies from 1–5% [1, 2].

The patients with beta thalassemia major suffer from chronic anemia due to hemolysis and ineffective erythropoiesis. Therefore, regular blood (erythrocytes) transfusions to maintain the pre transfusion hemoglobin concentration between 9.5 and 10.5 g/dL is essential for their survival and avoidance of complications. But, frequent transfusions result in inevitable accumulation of iron. Patients may accumulate 5 g of iron per year following transfusion of 25 units of blood per year. Increased gastrointestinal iron absorption due to increased hepcidin in thalassemia patients, cause further accumulation of iron. As a consequence of progressive iron overload, the iron binding protein; transferrin exceeds its capacity to bind with circulating free iron, releasing non transferrin bound iron into the blood circulation. The non-transferrin bound iron is unstable and exchange from ferric to ferrous status generating reactive oxygen species (ROS). Accumulation of free radicals, due to iron overload leads to lipid peroxidation and generation of both saturated and unsaturated aldehydes, causing cell damage [10, 11]. Progressive deposition of iron leads to dysfunction and failure of the major organs including heart, liver and endocrine glands such as pituitary, thyroid, parathyroid, adrenal and endocrine pancreas. Therefore, proper iron chelation therapy is mandatory for transfused patients with beta thalassemia major [3–11].

Patients with poor compliance to chelation therapy develop complications of iron overload including cardiac failure [12], cirrhosis [13], growth retardation [14], delay in sexual maturation [14], diabetes mellitus [15], hypothyroidism, hypoparathyroidism and osteopenia [15]. However lifelong administration of iron chelation regimens has posed challenges to clinicians and patients equally [16]. Poor compliance to chelation therapy and severe iron overload among patients has been reported in both developed and developing countries including United States [17], Pakistan [18], Egypt [19], India [20], Japan [21], Italy [22] and Dubai [23].

Therefore, regular assessment of iron status is essential for the efficient management of iron overload of beta thalassemia major patients. Serum ferritin level correlates with the iron burden in the body [24]. Serial measurements of serum ferritin level are widely used worldwide as an easy and reliable method of assessing the iron status in patients.

As a consequence of disturbed iron metabolism, growth failure is common among children and adolescents in multi-transfused beta thalassemia major patients which is due to many factors such as chronic anemia, iron over load, deficiency of growth hormone and thyroid hormone, chelation therapy and zinc deficiency.

Previous studies have shown a significant relationship between high serum ferritin level and growth failure of the beta thalassemia major patients [25, 26].

The aim of this study is to evaluate the iron overload and growth status of the beta thalassemia patients in one of the thalassemia centres in Sri Lanka and to find out the relationship between them.

MATERIALS AND METHODS

Study Design

This was a cross sectional study conducted on iron overload of the transfusion dependent beta thalassemia major patients at Paediatric Unit, Peradeniya Teaching Hospital in Sri Lanka during the period, 01 January 2014 to 31 December 2014.

Subjects

The study population consisted of 40 children of both genders with confirmed diagnosis of beta thalassemia major under any chelation regimen. All the patients are in the age group between 2 and 20 years. The diagnosis of beta thalassemia major was confirmed either by hemoglobin electrophoresis profiles or HPLC. Exclusion criteria included abnormal liver or renal functions, presence of acute infections at the time of blood collection. This study was approved by Ethical Review Committee, Faculty of Medicine, University of Peradeniya (2013/EC/43). The written consents were obtained from all the guardians of patients allowing their children to participate in the study.

Methodology

A standardized and validated questionnaire was used by the interviewer to gather information from all the patients during their hospital stay for regular blood transfusion. The questionnaire was pre tested with some patients in the pediatric unit of Peradeniya teaching hospital to ensure its feasibility and accuracy.

Assessment of mean pretransfusion hemoglobin level

The pretransfusion hemoglobin level which was measured by Drabskin method was taken from the past medical records of the patients. The pretransfusion levels over one year period were traced and the average was considered as the mean pretransfusion hemoglobin level.

Assessment of delayed puberty

Delayed puberty was diagnosed in boys and girls by absence of testicular development by age of 14 years and the absence of breast development by the age of 13 years respectively [27, 28].

Measurement of anthropometric parameters

Height of each patient was measured using a standard stadiometer. Weight was measured with light clothes using a standardized digital bathroom body weight scale. The z-scores for height and BMI were calculated by standard equations provided by World Health Organization [29].

$$\text{Z-score}(\text{height}) = \frac{(\text{Observed value}) - (\text{Median reference value})}{\text{Z-score value for reference population}}$$

$$\text{Z-score}(\text{BMI}) = \frac{(\text{Observed value} \div \text{M})^{\text{L}} - 1}{\text{L} \times \text{S}}$$

In this formula L, M and S values are for the reference population. M is the reference median value which estimates the population mean. L is the power needed to transform the data in order to remove skewness (i.e., to normalize the data). S is the coefficient of variation (or equivalent).The reference values for z-score for height and BMI were taken from the WHO standards [29].

Analysis of serum ferritin level

Blood samples (5 ml) were collected and centrifuged to separate serum. The serum was stored in -60°C until analysis. Serum ferritin level was analysed by enzyme linked immunosorbent assay (ELISA) kit (Fortress Diagnostics, Antrim, United Kingdom). The lower cut point for serum ferritin concentration for children is taken as 12 ng/dl [30].

Statistical analysis

The data was analysed by SPSS 16.0 statistical software (Softonic, Barcelona, Spain). The subjects were categorized into two groups based on their mean serum ferritin levels which are less than 3000 ng/ml and more than or equivalent to 3000 ng/ml. Student *t*-test was used to compare the groups. Correlations between iron overload and growth parameters were assessed using the Pearson correlation test. The p-values of less than 0.05 were considered statistically significant.

RESULTS

This study included 40 patients suffering from beta thalassemia major, with 22 (55%) females and 18 (45%) males. The mean age was 10.97±5.9 years with a range of 2–20 years. The duration of blood transfusion ranged from 14–235 months with a mean of 125.82±70.53. The median age at the first transfusion was six months (range 2–18 months) and the mean transfusion requirement was 265.01 ml/kg every year (range 379.1–500.0 ml/kg/year). The mean pretransfusion hemoglobin concentration was 8.15±1.21g/dl with a range of 4.00–10.3 g/dl and 37 patients (92.5%) were below the expected minimum hemoglobin concentration (9.5 g/dl). During the time of this study, all the patients were under deferasirox therapy and before 2010 they were on deferoxamine and deferiprone therapy. The current mean dose of deferasirox iron chelation therapy was 22.5±4.5 mg/kg/day.

The mean serum ferritin concentration was 2992.2±1575.35 ng/ml (range 875.5–7625 ng/ml). The ferritin concentration was less than 1500 ng/ml in six patients (15%) and 20 patients (50%) were with serum ferritin levels between 2500–5000 ng/ml. Majority of the patients with high serum ferritin concentration (>2500 ng/ml) were aged more than 10 years. Mean serum ferritin concentration of the females patients was 3057.54±1474.05 while in male patients it was 2924.55±1592.76. There was no significant difference of mean serum ferritin concentration between two groups (p = 0.78).

There was a significant relationship between iron overload with the age and the duration of blood transfusion of the patients (<0.05). Blood transfusion volume (ml//kg/year), mean pretransfusion hemoglobin concentration and method of chelation showed no relationship with mean serum ferritin concentration (>0.05) (Table 1).

The most common endocrine complication among the older patients (>12 years old) in the study group was delayed puberty (n = 10, 66.7%) (Younger patients <12 years were not considered when calculating the prevalence). Moreover, in this study, it was found that the mean z-score for height is –2.3±1.06 (range –0.75 to –5.06). Out of 40 patients, 20 (50%) were stunted (z-score for height <-2 SD) and 10 (25%) of them were severely stunted (z-score for height <-3 SD). Only 20 (50%) patients were of normal height (z-score for height ÿ-2SD) (Table 2).

The mean z-score for BMI is -1.32±1.28 (range 0.88 to -3.82). Out of 40 thalassemia patients, 35 % (14) were wasted (z-score for BMI <-2SD) and 7.5% (3) of them were severely wasted (z-score for BMI<-3SD) and the remaining were normal (z-score for BMI ÿ-2SD) (Table 2). There was no significant correlation between mean ferritin concentration and z-scores for height (p = 0.32, r = –0.16) and BMI (p = 0.78, r = 0.28)

In this study, it was found that 57.8% (11) of children below 10 years old were of normal height and 78.9% (15) were of normal BMI. Out of the patients above 10 years old, 57% (12) were stunted and 48% (9) were wasted (Table 3). There was a significant negative correlation between z-score for height and age of the patients (p = 0.02, r = –0.3).

DISCUSSION

Beta thalassemia major is a common hereditary hemoglobinopathy in Sri Lanka. Iron overload and growth retardation are common secondary complications in multi-transfused thalassemia patients. Therefore, effective iron chelation and close monitoring of iron burden is crucial in these patients. The measurement of

serum ferritin concentration is used in this study to assess the iron status of the patients as it is an easy, cost effective and noninvasive indicator of iron overload.

In our study, iron burden and growth status of 40 beta thalassemia patients were evaluated. Beta thalassemia major patients should maintain their serum ferritin levels below 1500 ng/ml to minimize the possible complication of iron overload. In this study, only 15% of patients had values below 1500 ng/ml. It was reported that 12.5% of beta thalassemia major patients were with serum ferritin levels less than 1000 ng/ml in a study conducted in Bhopal, India [20]. However, a similar study conducted in Western India reported that only 2% of the patients were with serum ferritin level less than 1000 ng/ml [31].

The mean serum ferritin concentration of the patients was 2992.2±1575.35 ng/ml, which is significantly high when compared with 12–122 ng/ml, the recommended serum ferritin concentration in children [30]. Therefore, proper adherence to iron chelation therapy and close monitoring of iron burden is mandatory. However, a similar study conducted in 2000 in Colombo has reported even high mean serum ferritin level, 5743 ng/ml in a group of beta thalassemia major patents managed in Lady Ridgeway Hospital [32]. Introduction of deferasirox, a novel iron chelating drug with high compliance might attribute to this marked improvement of management of iron burden in Sri Lankan beta thalassemia patients. Moreover, similar studies carried out in other South Asian countries have reported high mean ferritin levels when compared to values of this study. Mean serum ferritin levels reported to be 4236.5 ng/ml, 6723 ng/ml and 3272.5 ng/ml in studies conducted in Pakistan [18], India [33] and Saudi Arabia [34] respectively. However, Cunningham et al. reported that serum ferritin level was 1696 ng/ml and Eghbali et al. reported that mean serum ferritin was 1927 ng/ml in studies conducted in North America [35] and Iran [36] respectively. These differences in iron overload can be explained by differences in health care standards of those countries and socio-economical background of the patients. The data on comparative serum ferritin levels of thalassemia major patients in different parts of the world is summarized in Table 4.

Since age and duration of blood transfusion showed a significant relationship with mean serum ferritin concentration, poor adherence to chelation therapy may lead to progressive iron overload in beta thalassemia major patients. Therefore, close monitoring of the iron burden and proper iron chelation therapy will be beneficial in management of beta thalassemia major patients.

As growth failure is a common secondary complication of multi-transfused beta thalassemia major patients who are under iron chelation therapy [37, 38], in addition to the iron burden, the growth status of the patients also was evaluated.

According to our study, 50% of the patients were stunted. Similar findings were reported in a study conducted in Egypt, which specified that 49% of multi-transfused beta thalassemia patients were stunted [37]. Moreover, Hashemi et al. observed 46% of beta

Table 1: The comparison of clinical variables between two groups (based on serum ferritin concentration) in beta thalassemia major patients

	Mean Ferritin concentration <3000 ng/ml Mean (SD)	Mean Ferritin concentration >=3000 ng/ml Mean (SD)	p-value
Mean age (years)	9.1±6.0	13.3±5.3	0.02*
Duration of blood transfusion (months)	103.7±72.7	152.8±62.3	0.03*
Blood transfusion volume (ml/kg/year)	256.8±65.8	270.2±84.3	0.57
Pretransfusion hemoglobin level (g/dl)	8.1±1.2	8.2±1.3	0.92
Deferasirox dose (mg/kg/day)	60.8±11.8	62.7±12.9	0.65

significant at p<0.05, Abbreviations: SD= Standard deviation

Table 2: Growth parameters and iron overload status in beta thalassemia major patients

Serum ferritin concentration (ng/ml)	Height for Age			Body mass index for Age		
	Normal	Mild stunting	Severe stunting	Normal	Mild wasting	Severe wasting
<1500	4 (66.6%)	1 (16.7%)	1 (16.7%)	4 (66.7%)	2 (33.3%)	0 (0%)
1500–<2500	5 (50%)	3 (30%)	2 (20%)	4 (40%)	4 (40%)	2 (20%)
2500–5000	9 (45%)	6 (30%)	5 (25%)	14 (70%)	5 (25%)	1 (5%)
>5000	2 (50%)	1 (25%)	1 (25%)	4 (100%)	0 (0%)	0 (0%)
Total	20 (50%)	10 (25%)	10 (25%)	26 (65%)	11 (27.5%)	3 (7.5%)

Table 3: Growth parameters in beta thalassemia major patients of different age groups

Age (Years)	Height for Age			Body mass index for Age		
	Normal	Mild stunting	Severe stunting	Normal	Mild wasting	Severe wasting
<5	5 (71.4%)	1 (14.2%)	1 (14.2%)	6 (85.7%)	1 (14.3%)	0 (0%)
5–10	6 (50%)	4 (33.3%)	2 (16.7%)	9 (75%)	3 (25%)	0 (0%)
>10	9 (42.9%)	5 (23.8%)	7 (33.3%)	11 (52.3%)	7 (33.3%)	3 (14.2%)

Table 4: Comparative serum ferritin levels

Reference	Country	Mean serum ferritin level	% of patients with serum ferritin level less than 1000ng/ml
Shah et al. [31]	Western India	-	2.00%
Mishra and Tiwaria [20]	Bhopal, India	-	12.5%
Lucas et al. [32]	Colombo, Sri-Lanka	5743 ng/ml	-
Choudhry et al. [33]	India	6723 ng/ml	-
Riaz et al. [18]	Pakistan	4236.5 ng/ml	-
Cunningham et al. [35]	North America	1696 ng/m	-
Eghbali et al. [36]	Iran	1927 ng/ml	-
Al Jaouni et al. [34]	Saudi Arabia	3272.5 ng/ml	-

thalassemia patients were stunted (<5th percentile) in a study conducted in Iran [25].

The height for age showed a significant negative correlation with the age. This suggests the development of short stature is highly associated with disease progression. Olivieri et al. reported that growth failure is associated with long-term use of deferoxamine therapy [39]. In the current study, all the older patients exceeding 10 years of age were under deferoxamine therapy before 2010 for longer duration when compared with the younger patients. However the association between short stature and long-term previous exposure to deferoxamine therapy cannot be established as several compounding factors like chronic anemia, zinc deficiency, high ferritin levels at their early childhood can affect the growth.

This study did not demonstrate any relationship between serum iron overload and short stature. Our results match with the findings of a study which specifies that there is no association between SD scores of height of the patients and degree of chelation [40]. The short stature among children in our group may be attributed to other contributing factors including genetic makeup, long-term use of iron chelators, chronic anemia and malnutrition due to poor socio-economic status of the patients. In contrast, many studies reported significant relationship between high serum ferritin levels and short stature [25, 26, 37]. However, we have not evaluated children's height in relation to mid parental height.

Delayed puberty is the most common endocrine complication observed among the older patients (>12 years old) of this study and short stature is more prevalent among the older patients. Therefore, delayed puberty might be associated with short stature.

In this study, it was revealed that 37% of the patients were wasted and similar study from Egypt revealed that 30% of the beta thalassemia major patients had significantly low BMI levels. Further, our results showed that low BMI values of the patients were not associated with either the age of the patients or high serum ferritin levels. Similarly, a study from India revealed that there is no correlation between physical growth and serum ferritin levels [38].

Patients in this study group have records of serum ferritin levels done regularly however lack of standardization prevail us from using such data. For the purpose of this study serum ferritin level was measured only once during the study due to financial constraints. However, single time point values of serum ferritin level may not reflect the status of iron overload accurately in beta thalassemia major patients. Furthermore, this might be the reason to the finding of no significant correlation between the serum ferritin and growth in this study.

Small sample size is another limitation of this study. Moreover, growth status of the age and sex matched healthy individuals was not assessed in this study. Therefore, more extensive multicenter studies with larger sample size are required in this regard.

CONCLUSION

This study concludes that the iron overload and growth retardation is common among beta thalassemia

major patients in Sri Lanka. But, there was no significant relationship between physical growth and iron overload in our situation. Therefore, it is important to evaluate the other contributing factors including chronic anemia, long-term use of chelators, genetic and socioeconomic makeup of the study group that may attribute to growth retardation in our patients. Further, proper management of iron overload is crucial to minimize the complications of beta thalassemia major patient and to increase their quality of life.

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Atthanayaka Mudiyanselage Dilhara Sewwandi Karunaratna – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published
JG Shirani Ranasingha – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Rasnayaka Mudiyanselage Mudiyanse – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
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Conflict of Interest
Authors declare no conflict of interest.

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