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...
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 Drabkins 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].

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

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

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 125.8±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 serum ferritin concentration of the females patients was 2924.55±1592.76 while in male patients it was 3057.54±1474.05. 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).

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 thalassemia patients to be stunted [37].

<table>
<thead>
<tr>
<th>Mean Ferritin concentration (ng/ml)</th>
<th>Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3000 ng/ml</td>
<td>9.1±6.0</td>
<td>13.3±5.3</td>
</tr>
<tr>
<td>&gt;=3000 ng/ml</td>
<td>152.8±62.3</td>
<td>270.2±84.3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Serum ferritin concentration (ng/ml)</th>
<th>Normal</th>
<th>Mild stunting</th>
<th>Severe stunting</th>
<th>Normal</th>
<th>Mild wasting</th>
<th>Severe wasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1500</td>
<td>4 (66.6%)</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>4 (66.7%)</td>
<td>2 (33.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1500–2500</td>
<td>5 (50%)</td>
<td>3 (30%)</td>
<td>2 (20%)</td>
<td>4 (40%)</td>
<td>4 (40%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>2500–5000</td>
<td>9 (45%)</td>
<td>6 (30%)</td>
<td>5 (25%)</td>
<td>14 (70%)</td>
<td>5 (25%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>&gt;5000</td>
<td>2 (50%)</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
<td>4 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (50%)</td>
<td>10 (25%)</td>
<td>10 (25%)</td>
<td>26 (65%)</td>
<td>11 (27.5%)</td>
<td>3 (7.5%)</td>
</tr>
</tbody>
</table>
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 several compounding factors like chronic anemia, zinc deficiency, high ferritin levels at their early childhood can affect the growth.

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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. 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

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

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Height for Age</th>
<th>Body mass index for Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Mild stunting</td>
</tr>
<tr>
<td>&lt;5</td>
<td>5 (71.4%)</td>
<td>1 (14.2%)</td>
</tr>
<tr>
<td>5–10</td>
<td>6 (50%)</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>9 (42.9%)</td>
<td>5 (23.8%)</td>
</tr>
</tbody>
</table>

### Table 4: Comparative serum ferritin levels

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Mean serum ferritin level</th>
<th>% of patients with serum ferritin level less than 1000ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al. [31]</td>
<td>Western India</td>
<td>-</td>
<td>2.00%</td>
</tr>
<tr>
<td>Mishra and Tiwaria [20]</td>
<td>Bhopal, India</td>
<td>-</td>
<td>12.5%</td>
</tr>
<tr>
<td>Lucas et al. [32]</td>
<td>Colombo, Sri-Lanka</td>
<td>5743 ng/ml</td>
<td>-</td>
</tr>
<tr>
<td>Choudhry et al. [33]</td>
<td>India</td>
<td>6723 ng/ml</td>
<td>-</td>
</tr>
<tr>
<td>Riaz et al. [18]</td>
<td>Pakistan</td>
<td>4236.5 ng/ml</td>
<td>-</td>
</tr>
<tr>
<td>Cunningham et al. [35]</td>
<td>North America</td>
<td>1696 ng/ml</td>
<td>-</td>
</tr>
<tr>
<td>Eghbali et al. [36]</td>
<td>Iran</td>
<td>1927 ng/ml</td>
<td>-</td>
</tr>
<tr>
<td>Al Jaouni et al. [34]</td>
<td>Saudi Arabia</td>
<td>3272.5 ng/ml</td>
<td>-</td>
</tr>
</tbody>
</table>
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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Author Contributions
Atthanayaka Mudiyanelage 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 Mudiyanelage 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
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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REFERENCES


