

Endocrine complications of beta-thalassemia major patients—Cross-sectional study

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ABSTRACT

Aims: To evaluate the prevalence of endocrine complications in beta thalassaemia major patients in one of thalassaemia treatment units in Sri Lanka. **Methods:** The patients (n = 40) aged >2 years admitted to the Teaching Hospital Peradeniya during the period of December 2013 to December 2014, under the treatment of iron chelation drugs were recruited for the study. The patients were interviewed for the sociodemographic variables and the data regarding endocrine complications were gathered from medical records. Anthropometric (height and weight) measurements and pubertal status were assessed by a qualified medical officer. The data were statistically analyzed by SPSS version 21. **Results:** The mean age of the patients was 10.97±5.9 years (range 2–20). The most common endocrine complication was a pubertal delay (53%). The prevalence of short stature, hypothyroidism, diabetes mellitus, and

hypoparathyroidism were 50%, 10%, 5%, and 2.5%, respectively. All the patients with endocrine complications were older children (>10-year-olds). **Conclusion:** Endocrine complications were common among the studied group of beta-thalassaemia major patients and it is related to progression of age. Regular assessment of endocrine function is imperative in the proper management of beta-thalassemia major patients.

Keywords: Beta-thalassemia major, Endocrine complications, Short stature

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INTRODUCTION

Beta-thalassemia major is an inherited disorder characterized by absence or inadequacy of beta globin chain synthesis. It is the most common monogenic hereditary hemoglobin disorder, which poses a major health burden in Sri Lanka [1].

Globally, 300,000–400,000 babies are born with sickle cell disease and thalassemia. According to most recent studies, it is estimated that 1.5% of global population are carriers of beta thalassemia and approximate number

of annual births of severe forms of beta thalassemia ranges from 50,000 to 60,000 [2].

The national incidence of 60–80 cases per year [3] together with the estimated life span of 20–25 years has resulted in a patient load exceeding 2000 patients. The prevalence of beta thalassemia trait among Sri Lankan population varies in different parts of the country from 1% to 5% [1].

Thalassemia patients suffer from chronic anemia due to hemolysis and ineffective erythropoiesis. Therefore, lifelong blood transfusion therapy together with iron chelation therapy is mandatory. Studies done in America, Pakistan, and Egypt showed high serum ferritin levels among thalassemia patients [4–6]. Therefore, despite advances in novel iron chelation therapy regimes, iron overload is the most common secondary complication among thalassemia patients.

Endocrine complications, such as hypogonadism, hypothyroidism, hypoparathyroidism, and pancreatic and adrenal insufficiency, are frequently observed among the thalassemia patients [7, 8]. Delayed puberty, growth retardation, diabetes, and hypogonadism are among the most prevalent manifestations of endocrinopathies. Hypothyroidism also observed frequently among thalassemia patients [9, 10]. The rate of diabetes among thalassemia patients has been reported to range from 2.3% to 24% [11, 12]. Hypoparathyroidism is known to occur rarely among thalassemia patients [11, 12].

Iron toxicity in endocrine glands mainly attributes to endocrinopathies among thalassemia patients [8]. Therefore, most of the time endocrine abnormalities are diagnosed during the second decade of life with the progression of iron deposition. Apart from iron toxicity, other factors including chronic anemia, zinc deficiency, and toxicity of iron chelating agents play a causative role in endocrinopathies.

Although, the prevalence of endocrinopathies among beta-thalassemia major patients were well studied in developed countries data of developing countries is limited. However, due to differences in healthcare standards and genetic makeup, national-level statistics of endocrinopathies might differ from those of developed countries. Moreover, prompt diagnosis and treatment of endocrine complications are imperative to improve the life span and quality of life of beta thalassemia major patients.

Therefore, the aim of this study is to evaluate the frequency of endocrine complications in a group of beta-thalassemia major patients at Teaching Hospital, Peradeniya in Sri Lanka and to identify the associated factors of endocrinopathies.

MATERIALS AND METHODS

Study setting

This is a cross-sectional study conducted on endocrine complications of the transfusion dependent beta-

thalassemia major patients under iron chelation therapy at one of the thalassemia treating unit at Teaching Hospital, Peradeniya in Sri Lanka during the period from January to December, 2014. The ethical approval was obtained from ethical review committee, Faculty of Medicine, University of Peradeniya (2013/EC/43).

Subjects

A total of 40 patients aged >2-year-olds with confirmed diagnosis of beta-thalassemia major under iron chelation therapy were recruited to the study. The diagnosis of beta thalassemia major disease was made by reduced or absent HbA, elevated levels of HbA₂, and increased HbF which is detected by haemoglobin electrophoresis and high performance liquid chromatography (HPLC). The patients with abnormal liver and renal functions and acute infections were excluded from the study. The written consent was obtained from the guardians of the patients and controls before recruitment.

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 medical histories were obtained from hospital files. The questionnaire was pretested with few patients in the pediatric unit of Peradeniya Teaching Hospital to ensure its feasibility and accuracy.

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

Hypoparathyroidism was diagnosed by low levels of serum calcium and high serum phosphates levels. Diabetes mellitus was screened by postprandial blood sugar and diagnosis was confirmed by the fasting blood glucose level more than 120 g/dL. Hypothyroidism was diagnosed by a high serum thyroid stimulating hormone (TSH) 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 analyzed by enzyme linked immunosorbent assay (ELISA) kits (Fortress Diagnostics, Antrim, United Kingdom).

Measurement of anthropometric parameters

We followed the methods of Karunaratna et al. 2017 [15]. 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 body mass index (BMI) were calculated by standard equations provided by World Health Organization [16].

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

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

In this formula *L*, *M*, and *S* values are for the reference population. *M* is the reference median value which estimates the population means.

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 World Health Organization (WHO) standards [17].

The lower body segment is measured by taking the length from the pubic symphysis to the floor. The upper body segment (sitting height) was calculated using the equation (Upper body segment = Total height – Lower body segment). The reference values for the calculation of the Z-score sitting height index was taken from the National Health and Nutrition Examination Survey (NHANS) III, United States [18].

The mid-arm circumference was measured at the mid-point between the tip of the shoulder and the tip of the elbow using a measuring tape in centimeters. The percentiles for mid upper arm circumference were calculated using the reference values given by the National Health Statistics Report, United States [19].

Statistical analysis

The data were edited, entered and analyzed by SPSS, version 21 (IBM SPSS® software, Chicago, US). The basic descriptive statistical analysis including measures of central tendency (Mean) and dispersion (Standard deviation) was done. Patients were statistically compared based on the presence of endocrinopathies. Correlations between parameters were analyzed by Pearson’s linear correlation test. Normality of distribution of data was checked by Kolmogorov–Smirnov test. Nonparametric data were analyzed using Mann–Whitney *U* test. The

data were analyzed by SPSS, version 21. The data were taken as statistically significant at p value 0.05.

RESULTS

Forty patients suffering from beta thalassemia major and thirty age and sex matched healthy individuals were included in the study. The male female ratio of the study group is 82:100 and the control group was 87.5:100. The mean ages of the patient group and control group were 11 ± 6 and 13 ± 6, respectively.

The commonest endocrine complication in the study group was delayed puberty. Out of 17 patients 53% showed delayed puberty. 71.4% of boys above 14 years showed pubertal delay (n = 5, 71.4%). Among females above 13 years 40% showed delayed puberty (n = 4, 40%).

Hypothyroidism was present in 4 (10%) patients. Diabetes mellitus was reported in 2 (5%) patients. Hypoparathyroidism was reported in 1 (2.5%) patient. There was a significant relationship between endocrine complications with the age and the period under of blood transfusion of the patients at p-value 0.05. Blood transfusion volume (mL/kg/year), mean pretransfusion hemoglobin concentration and deferasirox dose bear no relationship with endocrine complications (Table 1).

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). A total of 20(50%) patients were of normal height (Z-score for height ≥-2 SD) (Table 2). The mean Z-score for BMI is -1.32 ± 1.28 (range 0.88 to -3.82). Out of 40 thalassemia patients, 14 (35%) were wasted (Z-score for BMI <-2 SD) and 3(7.5%) of them were severely wasted (Z-score for BMI<-3SD) and the rest were normal (Z-score for BMI ≥-2SD) (Table 3). The prevalence of wasting and stunting among children of 5–18 years old is 26.7% and 13.1%, respectively [20].

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

Clinical parameter	Patients with one or more endocrine complications [#]	Patients with none of the endocrine complications studied [#]	p-value [#]
Mean age (years)	17.70±2.36	9.03±5.22	0.00**
Duration of blood transfusion (months)	203.4±26.61	103.17±63.34	0.00**
Blood transfusion volume (mL/kg/year)	298.27±104.72	251.88±59.99	0.36
Pre transfusion haemoglobin level (g/dL)	7.53±1.62	8.34±0.98	0.27
Deferasirox dose(mg/kg/day)	23.04±5.38	22.05±4.09	0.40
Mean serum ferritin level	3438.00±1699.08	2850.8±1442.76	0.29

**Significant at p = 0.001

[#]Mann–Whitney *U* test

Table 2: Height of the patients of different age groups

Age (years)	Height for age				Total
	Normal	Mild stunting	Moderate stunting	Severe stunting	
<5	5 (71.4%)	0 (0%)	1(14.3%)	1 (14.2%)	7
5–10	6 (50%)	3 (25%)	1(8.3%)	2 (16.7%)	12
>10	9 (42.9%)	3 (14.3%)	2(9.5%)	7 (33.3%)	21
Total	20	6	4	10	40

Table 3: BMI of the patients of different age groups

Age (years)	BMI for age			
	Normal n (%)	Mild wasting/thinning n (%)	Moderate wasting/thinning n (%)	Severe wasting/thinning n (%)
<5	6 (85.7%)	0(0%)	1 (14.3%)	0 (0%)
5–10	9 (75%)	2 (16.7%)	1(8.3%)	0 (0%)
>10	11 (52.3%)	1 (4.8%)	6(28.6%)	3 (14.2%)
Total	26	3	8	3

Therefore, the prevalence of wasting and stunting is significantly high among the beta thalassemia major patients when compared to the normal population ($p < 0.001$).

The majority of the patients ($n = 27, 67.5\%$) were with mid-upper arm circumference (MUAC) less than 5th percentile while none of them had MUAC exceeding a 50th percentile. The percentage of patients with MUAC below 5th percentile was higher among older children (>10 years) (66.7%) than younger patients (<10 years) (33.3%).

Z-score for height bear significant negative correlation with age of the patients ($p = 0.02$). There was no significant correlation between Z-score for BMI and age of the patients ($p = 0.17$). Z-score values for height bears significant negative correlation with period under blood transfusion therapy and blood its volume (Table 4). However, pretransfusion hemoglobin level and deferasirox dose bear no significant correlation with growth parameters (Tables 4 and 5). Although Z-score values for height had obvious negative relationship with serum ferritin concentration, it was not statistically significant.

DISCUSSION

Endocrine dysfunction is a common secondary complication that is associated with substantial morbidities and mortalities among beta-thalassemia major patients [10]. In our study, it was evident that the occurrence of endocrine complications was obviously related to the advancement of age (>10 years old).

Table 4: Correlation of Z-score for height with clinical parameters of the patients

Clinical parameter	r	p^{α}
Period under blood transfusion therapy (months)	-0.4	0.02*
Blood transfusion volume (mL/kg/year)	-0.3	0.03*
Pre transfusion hemoglobin level (g/dL)	0.1	0.69
Deferasirox dose (mg/kg/day)	-0.1	0.48

α Pearson's correlation test

*Significant at p value 0.05

Table 5: Correlation of Z-score for BMI with clinical parameters of the patients

Clinical parameter	r	p^{α}
Period under blood transfusion therapy (months)	-0.2	0.16
Blood transfusion volume (mL/kg/year)	-0.2	0.21
Pre transfusion haemoglobin level (g/dL)	0.2	0.34
Deferasirox dose (mg/kg/day)	-0.2	0.33

α Pearson's correlation test

Similarly, a group of Italian researchers has found that the majority of the patients with endocrine disorders were in their second and third decades of life [12]. This might be related to iron toxicity to endocrine organs due to the progression of iron deposition. Therefore evaluation of endocrine function in the second decade of life is mandatory in beta thalassemia major patients.

According to our study, 50% of the patients were stunted. Our results were with the agreement of studies conducted in Iran and Egypt which reported 49% and 46% of stunting respectively [21, 22]. Short stature showed a significant negative correlation with the age of the patients. In our study, it was revealed that 37% of the patients were wasted. A similar study from Egypt revealed that 30% of the beta-thalassemia major patients were having significantly low BMI levels [21]. Further, our results have shown 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 [23]. The majority of the patients (67.5%) were having MUAC less than <5th percentile. Therefore, according to MUAC majority of the patients were malnourished. Similar findings were observed by several researchers [24–26].

Delayed puberty was the commonest endocrine dysfunction observed in this study group (53.1%). Similar findings were reported by a multicenter study conducted by the International Thalassemia Federation which reported lack of pubertal changes in 40.5% of patients. In contrast, studies conducted in India and Iran reported that 68% and 71% of the patients were with impaired puberty respectively [9, 27, 28].

Ten percent of patient in this study were affected by Hypothyroidism compared to 17–18% in Iran [29] and 9% in North America [30].

Hypoparathyroidism which is a well-recognized endocrine abnormality in beta-thalassemia major disease was observed in only one patient (2.5%) in our study group. Our findings were consistent with the prevalence observed by Gabutti and Piga [31]. However, the percentage of patients with hypoparathyroidism in this study group was low when compared to other studies conducted in Oman and Iran which reported a prevalence of 14.6% and 19% respectively [32, 33].

Diabetes mellitus was observed in 5% of the patients in the study group. The prevalence of diabetes in this study group is consistent with the rate observed by Borgna-Pignatti et al. in an Italian cohort of patients [34]. A higher rate of diabetes (20%) is reported by Brittenham and coworkers [35].

The overall prevalence of endocrine complications in this study group is low when compared with regional and international studies. The mean age of the patients in our study group (10.97±5.9) is significantly less when compared to other studies. Moreover, all the patients were in their first and second decades of life. However, the development of endocrine dysfunction is associated with the progression of accumulation of iron in the endocrine glands with the advancement of age. Therefore, the low prevalence may be due to the young age of our patients. Furthermore, most of the other studies involved large cohort of the patients but in this study small number of patients were assessed. Variations in the rate of prevalence of endocrinopathies in different cohorts of patients might

be due to differences in health care standards and genetic makeup.

In this study, it was found that endocrine complications did not bear any significant association with iron overload. Our findings were consistent with studies that have reported no relation between the iron overload and endocrinopathies [19, 36, 37]. Therefore, endocrinopathies among thalassemia patients might be due to a combination of factors such as iron toxicity, chronic anemia and liver damage due to viral infections. Moreover, endocrine organ damage is caused by prolonged exposure of iron overload but the serum ferritin level indicates iron overload only in the last three months. Therefore, the serum ferritin levels is not an accurate indicator to assess the association between iron overload and endocrine organ dysfunction. In contrast, some researchers have found a significant relationship between endocrinopathies and serum ferritin level [8, 38, 39].

CONCLUSION

Routine assessment of endocrine functions is imperative in beta-thalassemia major patients after the age of 10 years. Moreover, adequate compliance to iron chelation therapy and maintenance of iron stores at safe levels is mandatory.

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Author Contributions

Attanayaka Mudiyanse Dilhara Sewwandi Karunaratna – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jamburagoda Gamage Shirani Ranasingha – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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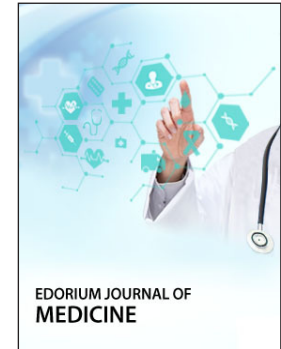
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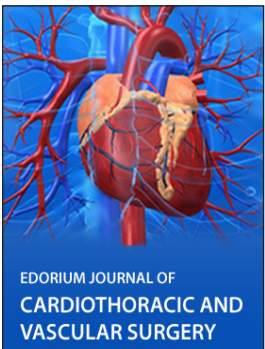
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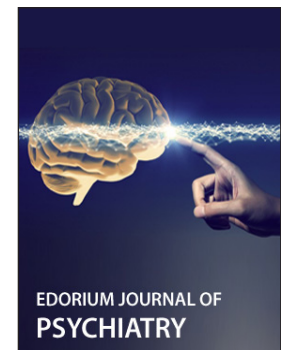
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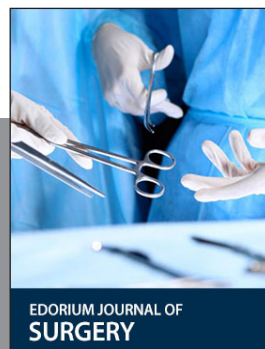
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