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Original Research Article

Thyroid hormone status in children with transfusion-dependent thalassemia

M. Abu Taleb[1]*, M. Abdur Rouf[2], Prodip Kumer[3], M. Rasel Bhuyan[4], Sumona Khandokar[3], M. Fakhrul Alam[3]

[1]Department of Paediatrics, Khwaja Yunus Ali Medical College and Hospital, Sirajganj, Bangladesh
[2]Department of Paediatrics, MH Samorita Medical College Hospital, Dhaka, Bangladesh
[3]Department of Paediatrics, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh
[4]Medical Officer (MCH-FP), Shahzadpur, Sirajgonj, Bangladesh

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***Correspondence:**
Dr. M. Abu Taleb,
E-mail: taleb047@gmail.com

ABSTRACT

Background: Thalassemia, a prevalent genetic disorder, necessitates recurrent blood transfusions for life, precipitating iron overload and premature death. In β-thalassemia major (BTM), hypothyroidism prevalence fluctuates (6-30%) globally, influenced by diverse chelation regimens. The objective of this study is to evaluate the thyroid hormone levels in pediatric patients diagnosed with transfusion-dependent thalassemia (TDT).
Methods: A hospital-based cross-sectional study was conducted at the paediatrics department of Sir Salimullah medical college Mitford hospital, Dhaka, focusing on TDT patients aged 4 to 18 years. Exclusions comprised known cases of hypothyroidism, children receiving hormonal therapy, those with a family history of hypothyroidism, and individuals with fewer than 10 blood transfusions. Serum separation involved centrifugation at 3000 rpm for 5 minutes, with subsequent aliquoting into two screw-capped dry clean vials: 1 ml each for FT4/TSH and serum ferritin estimation. Data were analyzed using SPSS version 24.0.
Results: Eighty-seven transfusion dependent thalassemia children aged between 4 to 18 years were chosen in this study. The hypothyroidism was seen in 7 (8%) patients. Of these, 4 (4.6%) participants were compensated hypothyroid and 3 (3.4%) participants were uncompensated hypothyroid. Most of the participants were hypothyroidism with Hb E-β thalassemia. The mean serum ferritin level was 2578.49±1385.06 ng/ml. Positive correlation of TSH with duration of disease (in years), total number of blood transfusion times and serum ferritin were statistically significant ($p<0.05$).
Conclusions: The present study demonstrates that 8% of the children with TDT have hypothyroidism. Hypothyroidism is more frequent among Hb E β-thalassemic children as compared to β-thalassemic children.

Keywords: Thyroid, Hormone, Children, Transfusion-dependent, Thalassemia

INTRODUCTION

Thalassemia is the most common genetic condition in the world.[1] β-thalassemia syndromes are genetic illnesses defined by a lack of β-globin chain synthesis, resulting in inefficient erythropoiesis. As a result, repeated blood transfusions are required to maintain life, which results in excessive iron deposition in numerous organs, resulting in early mortal.[2] A WHO report has shown that 3% of the population carries β-thalassemia and 4% carries Hb-E in Bangladesh.[3] Estimated that number of existing thalassemia patients in Bangladesh is about 100,000 and suspected total BTM and Hb-E β-thalassemia born around 1040 and 6443 per year respectively in country.[4]

The two main types of thalassemia are α-thalassemia and β-thalassemia respectively, with the former disrupting the synthesis of α-chains and the latter disrupting the synthesis of β-chains. The amount of Hb-A in the red cell decreases in β-thalassemia due to insufficient β-chain synthesis.[5] β-thalassemia is a group of recessively inherited hemoglobin diseases defined by a lack of β-globin chain production. The homozygous state causes severe anemia in infancy, necessitating repeated blood transfusions.[6] β-thalassemia is prevalent across a broad belt spanning the Mediterranean basin, the Middle East, the Indian subcontinent, Myanmar, and Southeast Asia.[7] The most severe form of β-thalassemia is β-thalassemia major, which is characterized by transfusion-dependent anemia.[8] The most frequent form of thalassemia in many Asian nations is caused by the inheritance of β-thalassemia and Hb E. Hb E is the most common hemoglobin variant in the eastern sections of the Indian subcontinent, Bangladesh, and other Southeast Asian countries.[9]

The clinical symptoms of Hb E-β thalassemia range in severity from thalassemia intermedia to severe TDT major.[8] The combination of blood transfusion and chelation therapy has significantly increased these patient's life expectancy, changing thalassemia from a rapidly fatal childhood condition to a chronic disease with a lengthy life.[10] On the other hand, frequent blood transfusions, iron overload, poor adherence to therapy, and the chronicity of the disease have all contributed to a wide range of complications in adolescents and young adults suffering from transfusion dependent thalassemia, including cardiac problems, hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism, and other endocrine and metabolic problems.[11] Following hypogonadism, hypothyroidism is the second most common endocrine disease. Regular blood transfusions and iron chelation with deferoxamine improved the disease's prognosis. So yet, the only definitive cure for thalassemia has been bone marrow transplantation, which became accessible in 1981, and technological breakthroughs continue to be documented.[12]

Thyroid hormones are essential determinants of the brain, somatic development in newborns, and metabolic activity in children and adults, affecting the function of nearly every organ. Thus, iron overload-related hypothyroidism can be either central or primary, depending on whether the iron is deposited on the pituitary, brain, or thyroid gland itself. Thyroid dysfunction has been described in patients with BTM, however, the severity and frequency vary depending on the chelation regimen.[13] Hypothyroidism is one of the most prevalent endocrine problems reported in patients with BTM. According to research, the prevalence and severity of the disease vary based on geography, management quality, and treatment methods. Overt hypothyroidism, subclinical hypothyroidism, and, in rare cases, central hypothyroidism have all been reported as thyroid dysfunction.[14] Other studies showed a significantly higher level of serum ferritin levels in the hypothyroid group as compared to the euthyroid group.[15] The main aim of this study is to determine the thyroid function status in transfusion- dependent thalassemic children that may create awareness among pediatricians about the necessity for evaluation of thyroid function in these patients.

Objectives

General objective

General objective was to assess the thyroid hormone status among children with TDT.

Specific objectives

Specific objectives were to evaluate the thyroid status of the study subjects by measuring FT4 and TSH, to find out the iron status by measuring the serum ferritin level, to compare serum ferritin, FT4, TSH between β-thalassemic and Hb E-β-thalassemic children, investigate FT4 correlation with age at diagnosis, disease duration, and age at first transfusion, serum ferritin, total transfusions, and iron chelator duration in TDT children and to observe the correlation of TSH with the above mentioned parameters.

METHODS

Study design

Cross-sectional study design was used.

Study period

The study was conducted over a period of one year from November 2021 to October 2022.

Place of study

Study conducted at the department of paediatrics, Sir Salimullah medical college Mitford hospital, Dhaka.

Study population

Diagnosed cases of transfusion-dependent thalassemic children aged 4 to 18 years were included in study.

Sampling method

Purposive non-random sampling method was used in the study.

Sample size calculation

The sample size was calculated by the following formula:

$$n = \frac{z^2 pq}{d^2}$$

Where,

n=Estimated sample size

Z=z value of standard normal distribution at 95% confidence level (1.96), p=estimated prevalence of the indicator

q=1-p

d=Desired precision (5% error)

From the literature, I found 6% hypothyroidism among transfusion-dependent β- Thalassemia children.[16] So, p value considered as 6% or 0.06. d=allowable error: 5%. Therefore, the sample size was,

$$n = \frac{1.96^2 \times 0.06\ (1 - 0.06)}{0.05^2}$$

$$= 86.6 \approx 87$$

According to formula sample size is 87.

Inclusion criteria

The inclusion criteria for this study require participants to be diagnosed with TDT and fall within the age range of 4 to 18 years. Additionally, they must have received a minimum of 10 blood transfusions.

Exclusion criteria

The exclusion criteria for this study involve children who are currently undergoing any form of hormonal therapy, those with a family history of hypothyroidism, individuals with a known case of hypothyroidism, and children suffering from other chronic illnesses.

Study procedure

A hospital-based cross-sectional study was conducted at Sir Salimullah medical college Mitford hospital, Dhaka, enrolling patients aged 4 to 18 diagnosed with TDT. Exclusions: known hypothyroidism, hormonal therapy, <10 blood transfusions. Diagnosis based on medical records and clinical examination. After meeting criteria, patients received unique IDs and obtained informed consent from legal guardians. Ethical clearance was obtained. Data collection involved comprehensive history-taking and clinical examination, recording demographic details, thalassemia history, iron chelation therapy, and family history. Measurements: weight using TANITA analog scale and height using a locally made height board without footwear.

Statistical analysis

After collection, data were entered into a personal computer for analyzing, plotting and presented in suitable tables and graphs. The statistical package for social sciences (SPSS) version 24 used for the analysis. The Shapiro-Wilk test was used to determine whether or not the data is normally distributed. The data reported as mean ± standard deviation (SD), median, or number (%) unless otherwise stated. Quantitative values were presented as mean ± standard deviation and were compared via the Mann-Whitney test. The level of statistical significance will be set to 0.05.

Ethical consideration

The researcher was concerned about the ethical issues relate to the study. In this study the following criteria were followed to ensure maintaining the ethical values. Formal ethical clearance was taken from the ethical review committee of the Sir Salimullah medical college Mitford hospital, Dhaka for conducting the study.

RESULTS

The cross-sectional study conducted in the paediatrics department, Sir Salimullah medical college Mitford hospital (SSMCMH), Dhaka from November 2021 to October 2022. Total 87 patients were selected by purposive non-random sampling technique. On the basis of inclusion and exclusion criteria, 4 to 18 years of age with transfusion dependent thalassemic children admitted in department of paediatrics SSMCMH were included during the specified period of time.

Table 1: Distribution of study participants according to age, (n=87).

Variables	N	Percentage (%)
Age (in years)		
4-8	49	56.3
9-13	36	41.4
14-18	2	2.3
Total	87	100.0
Mean ± SD	8.06±3.01	
Gender		
Male	47	54
Female	40	46

Table 1 is showing that the majority (49, 56.3%) of the participants with transfusion- dependent thalassemia were from 4-8 years of age. The mean ± SD of the participants was 8.06±3.013 years. The majority (47, 54%) of the patients were male.

Table 2: Distribution of study participants according to physical parameters, (n=87).

Physical parameters	Mean±SD
Height (cm)	113.80±16.03
Weight (kg)	19.02±7.53
BMI (kg/m^2)	14.22±2.95

From the above table II, we can say that, the mean height (cm), weight (kg), and BMI (kg/m^2) were 113.80±16.03 cm, 19.02±7.53 kg and 14.22±2.95 kg/m^2, respectively.

Figure 1 shows that, most patients (63, 72.4%) were suffering from Hb E β- thalassemia.

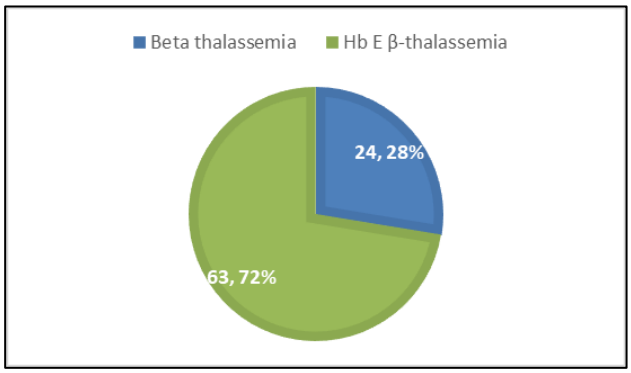

Figure 1: Distribution of study participants according to the type of thalassemia, (n=87).

Table 3: Distribution of study participants according to past medical history, (n=87).

Variables	Mean±SD
Age at first diagnosis (in months)	31.25±17.84
Duration of the disease (in years)	5.16±2.58
Age at first transfusion (in months)	33.40±17.16
Total number of blood transfusion times	48.27±24.15

Table 3 is showing that the mean age at first diagnosis was 31.25±17.84 months. The mean of duration of the disease was 5.16±2.58 years. The mean age at first transfusion was 33.40±17.16 months. The mean of total number of blood transfusion times was 48.27±24.15.

Table 4: Distribution of study participants according to the thyroid function, (n=87).

Thyroid function	Frequency	Percentage (%)
Euthyroid	80	92.0
Hypothyroidism	7	8
Compensated hypothyroidism	4	4.6
Uncompensated hypothyroidism	3	3.4

Table 4 is showing that most of the participants (80, 92%) were euthyroid. Hypothyroid were (7, 8%) participants among them (4, 4.6%) participants were compensated hypothyroid and (3, 3.4%) participants were uncompensated hypothyroid.

Table 5: Distribution of study participants according to type of thalassemia, (n=87).

Thalassemia type	Euthyroid, (n=80) (%)	Hypothyroidism, (n=7) (%)
Beta thalassemia	23 (28.75)	1(14.28)
Hb E β-thalassemia	57 (71.25)	6 (85.72)

Table 5 shows that majority of the Hb E-β thalassemic participants 85.72% (6) were hypothyroidism.

Table 6 shows that, serum ferritin level, serum FT4 level and serum TSH level were statistically and significantly different between beta thalassemia and Hb E β-thalassemic children ($p<0.05$).

Table 7 shows that TSH, duration of disease (in years), total number of blood transfusion times, and serum ferritin level were positively correlated and also the relation was statistically significant ($p<0.05$).

Table 6: Comparison of biochemical parameters between β-thalassemic and Hb E-β thalassemic children, (n=87).

Biochemical parameters	β-thalassemia, (n=24)	Hb E-β thalassemia, (n=63)	P value
	Mean±SD	Mean±SD	
Serum ferritin	2870.38±1222.57	2467.29±1435.61	0.015
Serum FT4	1.16±0.10	1.05±0.17	0.002
Serum TSH	2.99±0.81	2.65±1.47	0.007

Table 7: Correlation of TSH with different parameters in TDT children, (n=87).

Variables	TSH	
	R coefficient	P value
Age at first diagnosis (in months)	-0.196	0.069^{ns}
Duration of disease (in years)	0.368	0.000^{s}
Age at first transfusion (in months)	-0.111	0.306^{ns}
Total number of blood transfusion times	0.338	0.001^{s}
Duration of taking chelating agents (in months)	-0.034	0.783^{ns}
Serum ferritin	0.298	0.005^{s}

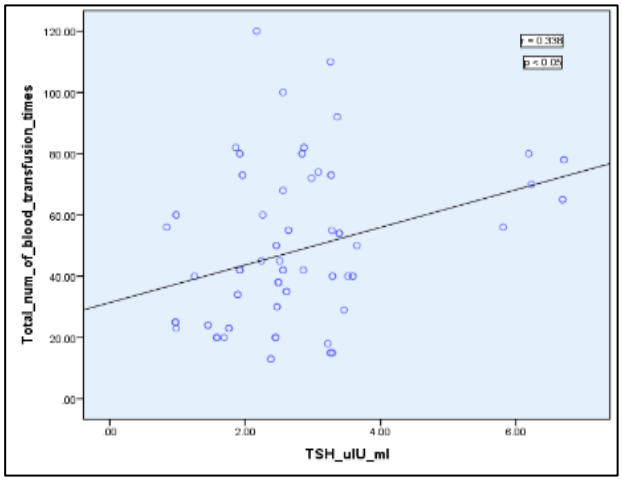

Figure 2: Scatter diagram showing a positive correlation between TSH and total number of blood transfusion times

Figure 2 shows that, TSH and total number of blood transfusion times were positively correlated and the relation was statistically significant (r=0.338, p<0.001).

DISCUSSION

This cross-sectional study was conducted with the aim to explore the thyroid hormone status in children with transfusion dependent thalassemia. A total number of 87 consecutive children were enrolled in this study. Study findings were discussed and compered with previously published relevant studies. We found in our study that, the majority (49, 56.3%) of the participants with TDT were from 4-8 years of age. The mean ± SD of the participants was 8.06±3.01 years. We also found that the majority (47, 54%) of the patients were male. One previous prospective cross-sectional study was conducted in India, they found the mean age was 9.49±4.82 years with minimum and maximum ages being 3 and 18 years, respectively.[16] They also found that out of a total of 50 beta-thalassemia children, 31 (62%) were male and 19 (38%) were female (p=0.090), which corresponds with the recent study findings. One cross-sectional study was carried out in Bangladesh, on that study shows the age of patients ranged from 4-15 years with a mean of 7.65±3.61 (±1SD), consists of 30 males and 20 females, which corresponds with the recent study findings.[17] We found in our study that, the mean height (cm), weight (kg), and BMI (kg/m^2) were 113.80±16.03 cm, 19.02±7.53 kg, and 14.22±2.95, respectively. A study was carried out, where mean height (centimeter) of cases and controls were 114.09±17.29 and 117.12±17.01 respectively (p<0.05). Mean weight (kgs) of cases and controls were 22.64±8.18 and 24.10±7.87 (p<0.05).[18] Compared to the control group, the studied patients had a lower mean height, weight, which is consistent with our study. We found in our study that; the majority of the patients (63, 72.4%) were suffering from Hb E β-thalassemia. A study found, 77.25% are Hb E β-thalassemia patients and 14.69% had Beta thalassemia major, and 8.06% other types.[9] Another study shows that 67% had Hb E β-thalassemia and 29% had BTM or intermedia, which is consistent with our present study.[19] Another study shows the mean serum ferritin level of the studied patient's was 2090.1±1701.7 ng/ml.[20] We found in our study that most of the participants (80, 92%) were euthyroid and (7, 8%) participants were hypothyroid among them (4, 4.6%) participants were compensated hypothyroid and (3, 3.4%) participants were uncompensated hypothyroid. In a study found in their study that the most common endocrine disorders were hypothyroidism was 9.17%, which corresponds with the recent study findings.[21] A study found hypothyroidism was 6% and no cases of clinical or central hypothyroidism, which is consistent with our study.[16] We found in our study that, serum ferritin level, serum FT4 level and serum TSH level were statistically and significantly different between β-thalassemia and Hb E-β thalassemia patients (p<0.05). This is a unique finding of this study. No other studies had brought up this finding till to date. In the present study, the age difference between the patients with normal thyroid function and those with thyroid dysfunction is statistically significant (p<0.05) consistent with a study were reported on comparison of euthyroid children with hypothyroid ones, they found that mean age in euthyroid group was 2.1 years whereas in hypothyroid group was 10.9 year, this was statistically significant.[22] We found in our study that, correlation of TSH with duration of disease (in years), total number of blood transfusion times, serum ferritin positively correlated and the statistically significant (p<0.05).

Limitations

As this is a small study conducted over a short period of time in one centre this may not reflect the real picture of whole country. We could not assess the FT3 level of the study participants in our study.

CONCLUSION

The present study demonstrates that 8% of the children with TDT have hypothyroidism that is more common in second decade of life. Hypothyroidism is more frequent among Hb E β-thalassemic children as compared to β-thalassemic children. Serum TSH is positively correlated with duration of disease, total number of blood transfusion times and serum ferritin level.

Recommendations

There needs multi-centric study with control group to understand the real picture of the disease prevalence. Early evaluation of thyroid function in transfusion dependent thalassemic children is needed as thyroid function may be impaired in these patients. In addition to iron chelation, therapy with L-thyroxin should be considered in hypothyroid thalassemia patients with moderate to severe iron overload.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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