Thyroid Status in Children with Transfusion Dependent Thalassemia in a Tertiary Level Hospital

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Most of the thalassemic children of Bangladesh are receiving repeated blood transfusion. But they do not receive chelation therapy due to financial constraints. As a result, iron overload occurs in various organs of these children. Extra iron that is loaded in thyroid gland causes thyroid dysfunction. This study was undertaken to evaluate thyroid status in children with transfusion dependent Thalassemia patient. This cross-sectional analytical study was conducted in the Department of Pediatrics, Mymensingh Medical College Hospital, Bangladesh from September 2016 to April 2018. Children having thalassemia diagnosed by Hb electrophoresis, aged 3-12 years of both sexes were included as study group. Children of same age and sex admitted in indoor of Mymensingh Medical College Hospital with minor illness and without thalassemia were taken as comparison group. Purposive Sampling technique was applied. Serum FT_4, TSH and ferritin level were estimated in all children. Data analysis was done with Statistical Package for Social Science (SPSS) version 21.0. A total of 60 patients were enrolled as study group and another 60 patients were compared as comparison group. Mean ages of study group was 7.88±2.55 years and comparison group were 7.22±2.48 years. The mean pre-transfusion hemoglobin, serum ferritin, serum FT_4 and serum TSH level were found 6.23±0.60 gm/dl, 2658.33±879.39 ng/ml, 15.14±4.40 fmol/mL, 4.29±4.60 µIU/mL respectively in study group. The mean serum FT_4 was found significantly lower and mean serum TSH was significantly higher in thalassemic children in comparison to non-thalassemic children (p= <0.05). Frequency of subclinical hypothyroidism was found significantly higher in study group (25.0%) compared to comparison group (3.3%) (p=0.001). Mean serum ferritin level was found significantly higher in hypothyroid cases. Mean FT_4 level was significantly lower and mean TSH level was significantly higher in hypothyroid thalassemic patients (p= <0.001). Significant positive correlation between serum ferritin level and serum TSH level was found. Higher serum ferritin level was found significantly associated with the development of hypothyroidism in thalassemic patients.

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Key words: Thyroid status, Children, Transfusion dependent, Thalassemia

Introduction

Thalassemia refers to a group of genetic disorders of globin chain production in which there is an imbalance between the alpha-globin and beta-globin chain production[1]. There are two main groups of thalassemia, one affecting the synthesis of α chains and the other affecting the synthesis of beta chains are called α thalassemia and β-thalassemia respectively. In β-thalassemia, the inadequate production of beta chains leads to a reduction in the amount of Hb-A in the red cell[2]. Hb-E with β-thalassemia is commonly seen in Bangladesh, α-thalassemia is rarely seen our country[1]. At the clinical level, β-thalassemia occurs classically in two forms: β-thalassemia major or Cooley's anemia, β-thalassemia minor or trait. Patients may be clinically classified as thalassemia intermedia if the severity of their disease lies between that of the major and minor forms[2]. Hb-E is one type of haemoglobinopathy, which is characterized by the production of defective Hb due to abnormalities in the formation of the globin moiety of the molecule[2]. In Hb-E β-thalassemia, one beta globin gene carries a thalassemia mutation in combination with a β-globin gene carries the point

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mutation encoding hemoglobin-E (βE/β-T genotype)[3]. Hb-E is caused by a substitution of glutamic acid by lysine in the 26th position of the β-globin gene[4]. WHO has estimated that about 1.5% the world's population might be carrier of β-thalassemia (β/βt) and about 60,000 severely affected infants are born every year. These individuals mostly originate from the Mediterranean, Middle East, Central Asia, India and Southern China[5]. The Maldives has the highest incidence of thalassemia in the world with a carrier state of 18.0% of the population. The estimated prevalence is 3.0-8.0% in populations from Bangladesh, China, India, Malaysia and Pakistan[6]. Among all thalassemia syndromes, Hb-E β-thalassemia is most common in our country and in South-East Asia. Hb-E syndrome carrier frequency in Bangladesh is 6.0%[7].

Thalassemia is commonly associated with the shortened erythrocyte life span and excessive destruction of erythrocytes. Therefore, blood transfusion is needed every 2-5 weeks, to maintain a pre-transfusion Hb level above 10 gm/dl[8]. Frequent blood transfusion in turn can result in increased iron stores of the body. So, after repeated blood transfusion, iron overload occurs in key organs- liver, heart and endocrine glands like thyroid, parathyroid, pancreas, anterior pituitary gland which results in dysfunction of these organs. As a consequence, they suffer from liver cirrhosis, heart failure, arrhythmia, hypothyroidism, hypoparathyroidism, diabetes mellitus, delayed puberty, growth retardation and so on. Most of these complications occur slowly and appear in the 2nd decade of the patient's life[2]. The commonest form of thyroid dysfunction seen in thalassemia is primary hypothyroidism due to dysfunction of the thyroid gland which leads to insufficient production of the thyroid hormones[9]. The frequency of hypothyroidism in thalassemic patients ranges from 6 to 30.0% among different countries depending on chelation regimens[10]. This study was conducted to evaluate thyroid status in children with transfusion dependent thalassemia.

Methods

This cross-sectional study was conducted in Department of Pediatrics from September 2016 to April 2018. Patients having thalassemia diagnosed by Hb electrophoresis, aged 3-12 years of both sex who were admitted in Department of Pediatrics, Mymensingh Medical College Hospital (MMCH) and Department of Blood transfusion (day care transfusion ward), MMCH with history of at least 10 times blood transfusions were taken as study group. Patients receiving less than 10 blood transfusions, having other comorbidities (Acute stroke syndrome, acute abdomen etc.) and hypothyroidism were excluded from the study. Sixty (60) patients diagnosed by Hb electrophoresis fulfilling the inclusion criteria were taken in study group. Sixty patients of same age and sex having minor illness like diarrhea, Pneumonia, UTI, viral fever was taken as comparison group. After proper explaining about objective and nature of the study, written informed consent was taken from the attendants who agreed to enroll their children in to the study. All the medical records carried by the patient were also scrutinized. Data regarding age, gender, type of thalassemia, age of first diagnosis and first transfusion, transfusion frequency, type and duration of taking of iron chelation therapy, adherence to chelation therapy, family history of thalassemia or thyroid disorder and their pre-transfusion Hb were recorded in the pre-formed standard data collection form. History about features of hypothyroidism also was taken and was noted in the data collection form. Detailed clinical examination was carried out. All studied patients were sent to Institute of Nuclear Medicine and Allied Sciences, Mymensingh. Then with all aseptic precaution 5ml of venous blood was drawn in the morning from each and every thalassemia cases and non-thalassemia comparison group for thyroid function tests (free T_4 and TSH Level) by using Radio Immuno Assay (RIA), Berthold, LB2111 Multicrystal Gamma Counter, Model no: 1053792, made in Germany method. At the same time, serum ferritin level of all thalassemic children were assessed by using Enzyme Immuno Assay (Biogen, GmbH model no: 6500, made in Germany). Serum TSH level >5.0 μIU/mL and free T_4 level <8.56 fmol/mL were considered as hypothyroidism. High serum TSH level (>5.0 μIU/mL) but normal free T_4 level (8.56-25.6 fmol/mL) were considered as sub clinical hypothyroidism. Data analysis was done with SPSS version 21.0. Significance was assessed at 5% level of significance. Comparison between quantitative values and qualitative values were tested by t-test and chi-square test respectively. Correlation of different values was done by using Pearson correlation coefficient. A probability (p)

value of <0.05 was considered statistically significant. This study was ethically approved by the Institutional Review Board (IRB) of Mymensingh Medical College, Mymensingh, Bangladesh with Memo no: MMC/IRB/2018/34 Dated: 13.01.2018.

Results

A total of 60 patients were enrolled as study group and another 60 patients were compared as comparison group. Age range of study population was 3-12 years. No significant statistical difference was found between mean ages of study group (7.88±2.55 years) and comparison group (7.22±2.48 years) p=0.149. Male was predominated in both groups. Male female ratio was 1.2: 1 in study group and 1.1:1 in comparison group. Weight and height of children were significantly lower in study group (p= <0.001). Mean weight for age Z score and mean height for age Z score were - 2.04±0.08 and - 2.74±0.28 respectively which were significantly lower than those of comparison group (p= <0.001) (Table I). The mean pre-transfusion hemoglobin, serum ferritin, serum FT_4 and serum TSH level were found 6.23±0.60 gm/dl, 2658.33±879.39 ng/ml, 15.14±4.40) fmol/mL, 4.29±4.60 μIU/mL respectively in study group. Hb-E was 66.7% β thalassemia and 33.3% were Thalassemia major (Table II). The mean serum FT_4 was found significantly lower and mean serum TSH was significantly higher in thalassemic children in comparison to non-thalassemic children (p= <0.05) (Table III). Thyroid dysfunction was found significantly higher in study group (25.0%) compared to comparison group (3.3%) (p=0.001) (Table IV) and all the thyroid dysfunction in our study were subclinical hypothyroidism. Among the patients having subclinical hypothyroidism 7 were male and 8 were female. No significant difference was found between mean age, sex, weight, height between hypothyroid (sub-clinical) and euthyroid cases. Mean age at first diagnosis and mean age at first blood transfusion were significantly lower in hypothyroid cases but total number of transfusions during illness was taken more in children with subclinical hypothyroidism (p= <0.05) (Table V). Mean serum ferritin level was found significantly higher among children with subclinical hypothyroidism. Mean FT_4 level was significantly lower and mean TSH level was significantly higher among thalassemic children with subclinical hypothyroidism (p= <0.001) (Table VI). Higher serum ferritin level was found significantly associated with hypothyroidism in thalassemic patients (Table VII). Significant positive correlation of serum ferritin level with age of the children (r=0.495, p= <0.001) (Table VIII) and serum TSH level (r=0.466, p= <0.001) was found (Figure 1). Significant negative correlation of serum ferritin level (r=-0.557, p= <0.001) and serum TSH level (r=-0.540, p= <0.001) were also observed with pre-transfusion haemoglobin level. Serum FT_4 was found positively correlated with pre-transfusion haemoglobin (r=0.367, p=0.004) and negatively correlated with serum TSH level (r=-0.541, p= <0.001) (Table VIII).

Table I: Comparison of demographic characteristics of studied children

Variables	Study group (n=60)	Comparison group (n=60)	p value
	n (%)	n (%)	
Age in years			
3-7	26 (43.3%)	33 (55.0%)	
8-10	34 (56.7%)	27 (45.0%)	0.149
Mean±SD	7.88±2.55	7.22±2.48	
Gender			
Male	33 (55.0%)	32 (53.3%)	
Female	27 (45.0%)	28 (46.7%)	
Male female ratio	1.2:1	1.1:1	
Weight in Kg (Mean±SD)	16.38 ±3.89	22.75±7.57	<0.001
Height in cm (Mean±SD)	110.82±12.90	121.0±13.14	<0.001
WAZ (Mean±SD)	-2.04±0.08	0.52±0.70	<0.001
HAZ (Mean±SD)	-2.74 ±0.28	-0.38±0.49	<0.001

Values of quantitative variables were presented as mean (standard deviation), p-value reached from unpaired t test.

Table II: Laboratory findings of Thalassemic children by blood sample analysis and Hb electrophoresis

Variables	Values (Mean±SD)
Pre-transfusion Hemoglobin (gm/dl)	6.23±0.60
Serum ferritin (ng/ml)	2658.33±879.39
Serum FT_4 (fmol/mL)	15.14±4.40
Serum TSH (μlU/mL)	4.29±4.60
Hb Electrophoresis [n (%)]	
Thalassemia major	15 (33.3)
Hb E-β thalassemia	45 (66.7)

Table III: Comparison of Mean FT_4 and TSH level of thalassemia group and comparison group

Variables	Study group (n=60)	Comparison group (n=60)	p value (unpaired t test)
	(Mean±SD)	(Mean±SD)	
Serum FT_4 (fmol/mL)	15.14±4.40	16.91±3.52	0.017
Serum TSH (μIU/mL)	4.29±4.60	2.01±1.09	<0.001

Table IV: Comparison of thyroid status between thalassemia and comparison group

Variables	Study group (n=60)	Comparison group (n=60)	p value (Chi square test)
	n (%)	n (%)	
Hypothyroid	15 (25.0)	02 (03.3)	0.001
Euthyroid	45 (75.0)	58 (96.7)	

Table V: Comparison of demographical and clinical characteristics between hypothyroid and euthyroid cases in thalassemia patients

Variables	Euthyroid (n=45)	Hypothyroid (n=15)	p value
	(Mean±SD)	(Mean±SD)	
Age in years	7.88±2.62	7.90±2.42	0.977
Sex			
Male [n (%)]	26 (57.8)	07 (46.7)	0.454
Female [n (%)]	19 (42.2)	08 (53.3)	
Weight in Kg	16.38±3.99	16.40±3.69	0.985
Height in cm	110.76±13.42	111.0±11.64	0.950
Age at first diagnosis (months)	31.38±17.23	16.13±10.38	0.003
Age at first blood transfusion (months)	32.07±17.23	18.13±9.43	0.004
Total duration of treatment (years)	5.0±2.1	05.6±02.4	<0.001
Total number of transfusions	35.46±12.84	48.87±11.10	0.001
Number of cases having affected family member [n (%)]	16 (35.6)	10 (66.7)	0.001

Table VI: Comparison of biochemical characteristics between hypothyroid and euthyroid cases in thalassemia patients

Biochemical characteristics	Euthyroid (n=45) (Mean±SD)	Hypothyroid (n=15) (Mean±SD)	p value (unpaired 't' test)
Pretransfusion hemoglobin (gm/dl)	6.42±0.57	5.65±0.14	<0.001
Serum ferritin (ng/ml)	2417.78±820.28	3380.33±632.68	0.020
Serum FT_4 (fmol/mL)	16.96±3.48	9.69±1.09	<0.001
Serum TSH (µIU/mL)	1.72±0.88	12.02±1.19	<0.001

Table VII: Thyroid status in thalassemia cases in relation to high serum ferritin level

Serum ferritin (ng/ml)	Euthyroid (n=45) n (%)	Hypothyroid (n=15) (n (%)	p value (chi-square test)
≥2000	31 (68.9)	15 (100.0)	0.014
<2000	14 (31.1)	00 (00.0)	

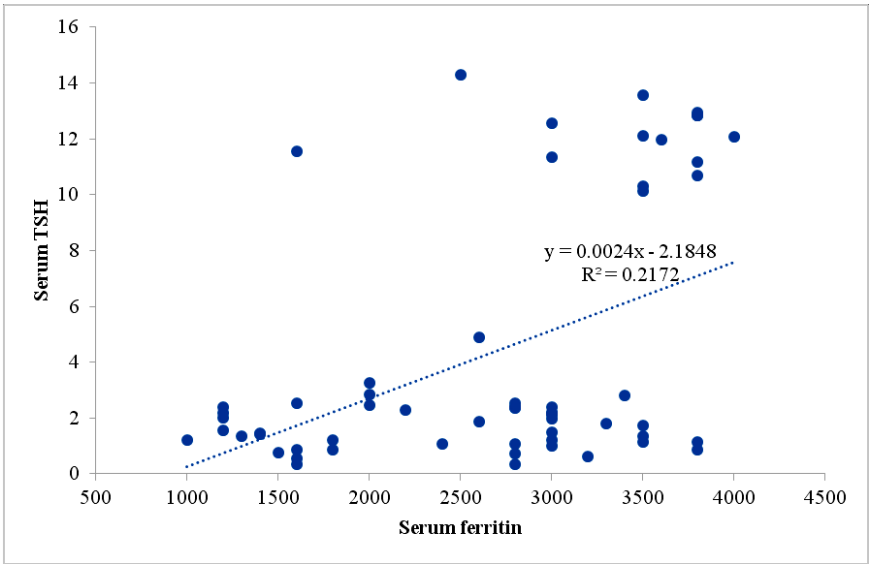

Figure 1: Correlation between serum ferritin and TSH level in thalassemia cases

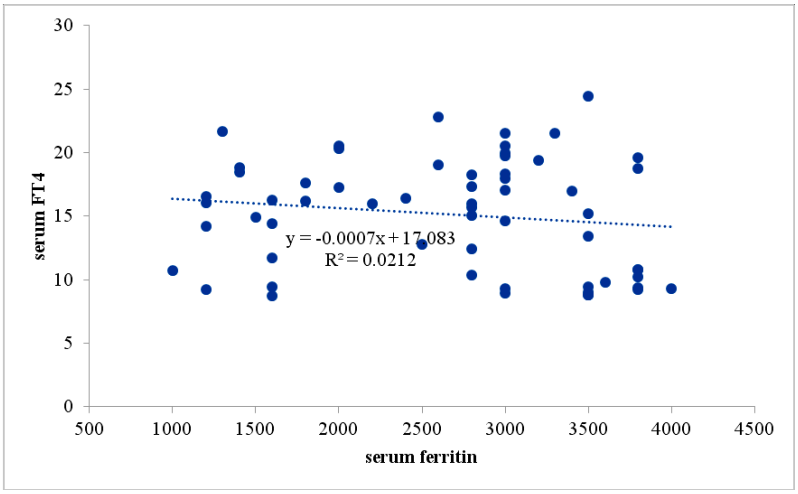

Figure 2: Correlation between serum ferritin and serum FT_4 level in thalassemia cases

Table VIII: Correlation between age, serum ferritin, FT_4, TSH and pre-transfusion hemoglobin level in thalassemia patients

		Age in years	Pre-Transfusion Hb (gm/dl)	Serum Ferritin level (ng/ml)	Serum FT_4 Level (fmol/mL)	Serum TSH Level (μIU/mL)
Age in years	Pearson correlation	1.0	-0.147	0.495*	-0.030	0.040
	p value	-	0.263	<0.001	0.745	0.664
Pre-Transfusion Hb (gm/dl)	Pearson correlation	-0.147	1	-0.557*	0.367*	-0.540*
	p value	0.263	-	<0.001	0.004	<0.01
Serum ferritin level (ng/ml)	Pearson correlation	0.495*	-0.557*	1	-0.146	0.466*
	p value	<0.001	<0.001	-	0.267	<0.001
Serum FT_4 Level (fmol/mL)	Pearson correlation	-0.030	0.367*	-0.146	1	-0.551*
	p value	0.745	0.004	0.267	-	<0.001
Serum TSH Level (μIU/mL)	Pearson correlation	0.040	-0.540*	0.466*	-0.541*	1
	p value	0.664	<0.001	<0.001	<0.001	-

*Correlation is significant at the 0.05 level (2-tailed).

Discussion

Iron overload of tissue is the most important complications of beta thalassemia and is a major subject of management. Iron overload is an important etiological factor in thyroid failure[11]. In the present study, 60 patients with transfusion dependent thalassemia were enrolled of which 15 cases (25.0%) were found to have subclinical hypothyroidism which was consistent with the observation of Sharmin et al.12. They reported the frequency of hypothyroidism in thalassemia patients of Bangladesh was 26.0%. Hypo-thyroidism was also reported in 17.6% of thalassemia patients in Thailand[13]. A little bit higher prevalence was reported in other studies like 36.0% by Farmaki[10] in Greece, 35.0% by Soliman et al.[14] in Qatar, 26.8% by Rindang et al.[15] in Jakarta. The differences in frequency may be due to different protocols of therapy. Subclinical hypothyroidism was the most prevalent in majority of studies[10,11,12,16] but clinically overt hypothyroidism was also found in different studies[14,17,18]. In this study, a significantly high proportion of subclinical hypothyroidism was found in thalassemia group (25.0%) compared to non-thalassemia comparison group (3.3%), this finding stroked us to find that there must be some other factors causing hypothyroidism in thalassemia than in normal population. Ghosh et al.[19] and Sharmin et al.[12] showed high serum ferritin levels and anaemic hypoxia as causes of hypothyroidism in thalasemic children. In this study, the mean serum ferritin level was statistically higher in hypothyroid cases than euthyroid cases (p=0.020) which was consistent with the observation of Ghosh et al.[19] Rindang et al.[15] reported in his study that regular and adequate use of iron chelation therapy decrease the chance of hypothyroidism due to iron overload. Age and sex did not keep any value in development of hypothyroidism in thalassemic patients in this study but number of total transfusions, age at first diagnosis, age at first transfusion has statistically significant association with frequency of hypothyroidism. Though the age of the patient with thalassemia was correlated significantly with FT_4 and ferritin level in some studies[14,15], the present study did not find any significant correlation of FT_4 with age but a significant correlation of age and serum ferritin level was found. The mean age of patient with hypothyroidism in this study was 7.90±2.42 years which is much lower in comparison to other study where they noted thyroid abnormalities as a

consequence of iron overload in second decade of life[14]. All of our hypothyroid cases were subclinical hypothyroidism (normal FT_4 but high TSH levels). Subclinical hypothyroidism was also detected in thalassemia below 10 years of life in some other studies[16,20,21]. The lower age in those studies may be due to inadequate chelation therapy, chronic anemia and malnutrition that is commoner in this part of the world. In this study a significant association between hypothyroidism and high serum ferritin level (>2000 ng/dL) was found. A significant positive correlation between serum ferritin level and serum TSH was also found in the present study which was consistent with previous studies[10,14,19,21]. Serum FT_4 level was shown decreased with increase in serum ferritin level but this correlation was not significant ($p>0.05$). Almost similar findings were observed by Ghosh et al.19. Interestingly, the present study found a significant difference in anemic status between euthyroid and hypothyroid thalassemia patient ($p= <0.001$). Sharmin et al.[12] also showed similar findings and thalassemia patients having more anemia could not maintain their normal thyroid function in their study. So, anemia causing hypoxia could be also responsible factor for causing damage to thyroid gland in thalassemia patients in the present study.

Conclusion

It could be concluded that the frequency of subclinical hypothyroidism in thalassemic patient was 25.0%. There was significant positive correlation between serum ferritin level and TSH level in thalassemic patients. Higher serum ferritin level was found significantly associated with the development of hypothyroidism in thalassemic patients. Thereby, thyroid function should be followed periodically for the early recognition of hypothyroidism and thus to improve the quality of life of thalassemia patients.

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