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Original Research Article

An Observational Study to Assess the Thyroid Function Status among the Transfusion Dependent Thalassemic Children

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Conflict of interest: Nil

Abstract:

Aim: The aim of the present study was to assess the thyroid function status among the transfusion dependent thalassemic children.

Material & Methods: This was a cross sectional study conducted in the Department of Paediatrics for a period of 18 months. A total number of 100 children with transfusion dependent thalassemia who met the inclusion and exclusion criteria were studied. Demographic data as well as history of blood transfusion and chelation therapy were collected. Thyroid function and iron load status were evaluated by measuring serum FT4, TSH and ferritin levels.

Results: Among them 28 (28%) were beta thalassemia major and 72 (72%) were Hb E beta thalassemia. Total male was 60 (60%) and female were 40 (40%). Mean weight and height were 33.67±10.42 kg and 132.4±13.4 cm respectively. Median weight for age Z score and median height for age Z score were -1.88 (-0.82 to -4.07) and -2.98 (-0.86 to -4.96) respectively. Mean BMI was 19.4±3.42 kg/m^2. The mean age at first diagnosis was 17.3 (±7.65) months, mean age at first blood transfusion was 18.22±7.53 months, mean total duration of disease was 10.90±4.02 years, and mean total number of blood transfusion was 81.7±33.4 units. History of thalassemia in other family members was found in 25 patients (25%). Euthyroid patients were 90 (90%) and hypothyroid patients were 10 (10%). Among hypothyroid patients 8 (8%) patients were compensated and 2 (2%) was uncompensated hypothyroidism. Significant association was found between higher serum ferritin level (≥2000 ng/ml) and hypothyroidism in thalassemia patients ($p<0.05$).

Conclusion: In the present study we documented hypothyroidism in transfusion dependent thalassemic children. Among them majority were compensated hypothyroidism. Higher number of blood transfusion and ferritin level ≥2000 ng/ml was found significantly associated with the development of hypothyroidism in thalassemic patients.

Keywords: Thyroid function, Transfusion dependent, Thalassemia.

Introduction

Beta-thalassemia major is an autosomal recessive hereditary anemia, which is incurable, caused by defective synthesis of hemoglobin, ineffective erythropoiesis and rapid erythrocyte breakdown, resulting in advanced heart failure and death in early childhood. [1,2] It is a group of hereditary blood disorders characterized by anomalies in the synthesis of the β chains of hemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. [3] The overall prevalence of β-thalassemia is 3–4 % with an estimate of around 8,000 to 10,000 new births with the major disease each year. [4,5] Disorders which are inherited and are characterized by deficiency in the production of beta globin chains resulting in ineffective erythropoiesis complicated by lack of affinity of circulating haemoglobin F to 2,3-diphosphoglycerate.

As a consequence of this, repeated blood transfusions are needed to maintain life, which in turn results in excessive iron being deposited in various organs resulting in early fatalities related complications including endocrine complication (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly,

adrenal glands), dilated myocardiopathy, liver fibrosis, and cirrhosis). [6] These complications are due to the toxic effects of the iron that gets deposited in the endocrine glands. In Beta Thalassemia Major (BTM) patients the frequency of hypothyroidism ranges from 6 to 30 % among various countries depending on chelation strategies. [7]

Thyroid dysfunction mainly occurs by gland infiltration, chronic tissue hypoxia, free radical injury, and organ siderosis. The thyroid gland is affected much before the thyroid-pituitary axis, which is less susceptible than the gonadal axis to iron induced damage. [8] Thyroid hormone is essential for the development and maintenance of normal function of CNS including brain development and its deficiency leads to mental retardation. So regular follow-up for early detection and timely treatment of such complications could improve the quality of life of these patients. Very few studies comparing the frequency of thyroid dysfunction in children presenting with Beta-thalassemia major have been done.

Hence this study was conducted to assess the thyroid function status among the transfusion dependent thalassemic children.

Material & Methods

A Cross-sectional observational study conducted at Department of Paediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India was carried out for the duration of 18 months.

Inclusion Criteria

- Patients diagnosed as transfusion dependent thalassemia (Beta thalassemia and Hb E/ beta thalassemia), age ranged from 5-18 years and received at least 10 times of blood transfusion were included in the study.

Exclusion Criteria

- Patients who received less than 10 times of blood transfusion, very ill and known case of hypothyroidism were excluded from the study.

Methodology

The patients and their parents were informed about the study design and its objectives. They were explained that there will be no physical or social risk for the participants other than the regular activity as done for admitted cases. They were also informed about freedom to participate or not to participate at any time. No incentive was given for participation. Informed written consent was taken. All the information remained confidential.

100 patients diagnosed by Hb electrophoresis fulfilling the inclusion criteria were taken as study group. Age of the patients were 5-18 years. Age, gender, type of thalassemia, age of first diagnosis and first transfusion, total number of transfusions, type and duration of iron chelation therapy, adherence to iron chelation therapy, and family history of thalassemia and thyroid disorder were recorded. Height and weight of the children were measured in standard procedure. 4 ml of venous blood was drawn aseptically on the morning of attendance for regular blood transfusion of thalassemic children. Serum free thyroxine (FT4), thyroid stimulating hormone (TSH) level and serum ferritin level were estimated by chemiluminescent immunoassay using the access Beckman Coulter analyser in the laboratory of microbiology department. On the basis of their thyroid profile the thalassemic patients were further divided into euthyroid, compensated hypothyroid and uncompensated hypothyroid.

Statistical Analysis: All data was recorded systematically in preformed data collection form. The entered data was checked, verified and analyzed by appropriate computer software. Statistical analysis was performed by using SPSS, version 21. Data were expressed as frequency, percentage, mean, standard deviation, median and range. The data was presented in tabular form. Appropriate statistical test was applied for data analysis. Categorical variables were compared by chi-squared test or Fischer's exact test. Unpaired t test was used to compare between two variables. Correlation was done by using Pearson correlation co-efficient. P value less than 0.05 was considered statistically significant.

Results

Table 1: Demographic and clinical characteristics of study population

Variables	Patients (%)
Age (mean±SD) (years)	11.49±3.82
Sex	
Female	40 (40)
Male	60 (60)
Weight (Mean ± SD) (kg)	33.67±10.42
Height (Mean ± SD) (cm)	132.4±13.4
WAZ median (range)	-1.88 (-0.82 to -4.07)
HAZ median (range)	-2.98 (-0.86 to -4.96)
BMI (Mean ± SD) (kg/m^2)	19.4±3.42

Type of thalassemia	
β thalassemia major	28 (28)
Hb E β thalassemia	72 (72)
Age at first diagnosis (Months)	16.4±7.63
Total duration of disease (Years)	10.90±4.02
Age at first blood transfusion (Months)	18.22±7.53
Total number of transfusions	81.7±33.4
Number of cases having affected family member	25 (25)
Number of cases received iron chelation therapy	72 (72)
Type of iron chelation therapy	
Deferiprone	71 (71)
Deferasirox	12 (12)
Deferiprone + Deferoxamine	5 (5)
Deferiprone + Deferasirox	12 (12)
Number of cases had good compliance to iron chelation	25 (25)
Duration of iron chelation therapy in months	16.94±14.58

Among them 28 (28%) were beta thalassemia major and 72 (72%) were Hb E beta thalassemia. Total male was 60 (60%) and female were 40 (40%). Mean weight and height were 33.67±10.42 kg and 132.4±13.4 cm respectively. Median weight for age Z score and median height for age Z score were -1.88 (-0.82 to -4.07) and -2.98 (-0.86 to -4.96) respectively. Mean BMI was 19.4±3.42 kg/m^2. The mean age at first diagnosis was 17.3 (±7.65) months, mean age at first blood transfusion was 18.22±7.53 months, mean total duration of disease was 10.90±4.02 years, and mean total number of blood transfusion was 81.7±33.4 units. History of thalassemia in other family members was found in 25 patients (25%).

Table 2: Thyroid function status in study population

Thyroid function status	N	Percentage (%)
Euthyroid	90	90
Hypothyroid		
Compensated	8	8
Uncompensated	2	2
Total	100	100

Euthyroid patients were 90 (90%) and hypothyroid patients were 10 (10%). Among hypothyroid patients 8 (8%) patients were compensated and 2 (2%) was uncompensated hypothyroidism.

Table 3: Serum ferritin levels

Serum ferritin (ng/ml)	Euthyroid, (n=90)	Hypothyroid, (n=10)	P-value
≥2000	55	10	0.025
<2000	35	0	

Significant association was found between higher serum ferritin level (≥2000 ng/ml) and hypothyroidism in thalassemia patients ($p<0.05$).

Table 4: Comparison of demographic and clinical characteristics between euthyroid and hypothyroid cases in thalassemia patients

Variables	Euthyroid, (n=90)	Hypothyroid, (n=10)	P value
Age (Years)	11.29±3.93	12.88±3.47	0.266
Sex			
Female	56	6	1.00
Male	34	4	
Weight (kg) (Mean ± SD)	32.38±10.5	35.65±8.52	0.314
Height (cm) (Mean ± SD)	128.4±14.46	134.6±12.18	0.620
WAZ	-2.04±0.76	-2.25±1.05	0.474
HAZ	-2.78±1.08	-3.43±0.82	0.088
Age at first diagnosis (months)	18.22±7.63	18±7.43	0.780
Total duration of disease (years)	11.78±4.04	12.06±3.87	0.110
Age at first blood transfusion (months)	18.12±7.73	20±5.4	0.748

Total no. of transfusions	79.8±26.4	124.4±38.4	<0.0001
No. of cases received iron chelation therapy	63	7	0.756
Duration of iron chelation therapy in months	16.8±14.86	12.34±10.55	0.172
No. of cases with good adherence to iron chelation therapy	30	1	0.135

No significant difference found in terms of mean age, sex, weight, height, WAZ score, HAZ score between euthyroid and hypothyroid cases. There was no significant difference in terms of age at first diagnosis (months), total duration of disease (years), age at first blood transfusion (months), number of cases received iron chelation therapy, duration of iron chelation therapy in months and number of cases with good compliance to iron chelation therapy between the two groups. Hypothyroid patients received significantly greater number of blood transfusions than euthyroid patients (p<0.0001).

Table 5: Mean values of ferritin, FT4 and TSH in euthyroid and hypothyroid patients

Mean values	Euthyroid, (n=90)	Hypothyroid, (n=10)	P value
Ferritin (ng/ml)	3614.6 (±2434.6)	4746.4 (±2024.6)	0.178
FT4 (ng/dl)	1.218 (±0.042)	1.038 (±0.242)	<0.0001
TSH (µIU/ml)	2.796 (±1.268)	7.956 (±1.584)	<0.0001

The mean ferritin level was higher in hypothyroid group than in euthyroid group but p value was not significant. Mean FT4 and TSH values were significantly different in euthyroid and hypothyroid groups (p≤0.0001).

Discussion

Thyroid hormones are critical determinants of brain and somatic development in infants and of metabolic activity in children; affecting the function of virtually every organ. Thyroid dysfunction has been reported in a number of studies on thalassemia patients. [9] Transfusion dependent thalassemia patients require regular blood transfusion to survive. Without adequate transfusion support, they would suffer several complications and a short life span. This category includes patients with β- thalassemia major and severe HbE β-thalassemia. [10]

Among them 28 (28%) were beta thalassemia major and 72 (72%) were Hb E beta thalassemia similar to the study done by Tahura et al [11] where HbE-β Thalassemia was found the commonest type of thalassemia among children. Total male was 60 (60%) and female were 40 (40%). Mean weight and height were 33.67±10.42 kg and 132.4±13.4 cm respectively. Median weight for age Z score and median height for age Z score were -1.88 (-0.82 to -4.07) and -2.98 (-0.86 to -4.96) respectively. Mean BMI was 19.4±3.42 kg/m^2. The mean age at first diagnosis was 17.3 (±7.65) months, mean age at first blood transfusion was 18.22±7.53 months, mean total duration of disease was 10.90±4.02 years, and mean total number of blood transfusion was 81.7±33.4 units. Kurtoglu et al [12] found 12.8% hypothyroidism cases in transfusion dependent thalassemia patients in Turkey which was consistent with the present study. Somchit et al [13] reported 17.6% hypothyroid cases in thalassemia patients. A study done by Karim AKMR et al [14] showed 20% patients with hypothyroidism, which was higher than the present study.

History of thalassemia in other family members was found in 25 patients (25%). Euthyroid patients were 90 (90%) and hypothyroid patients were 10 (10%). Among hypothyroid patients 8 (8%) patients were compensated and 2 (2%) was uncompensated hypothyroidism. Significant association was found between higher serum ferritin level (≥2000 ng/ml) and hypothyroidism in thalassemia patients (p<0.05) which was consistent with the studies done by Sharmin et al, Zervas et al, Farmaki and Agarwal et al. [15-18] Thyroid dysfunction is a frequently occurring endocrine complication in thalassemia major, but its prevalence and severity are variable and the natural history is poorly described. [19] Autoimmunity has no role in the pathogenesis of thalassemia related hypothyroidism. [20] Primary hypothyroidism is characterized by an elevated thyroid-stimulating hormone (TSH) level and decreased (low) T4. Secondary or central hypothyroidism is characterized by decreased T4 and low TSH. Up to 5% of thalassaemic patients develop overt clinical hypothyroidism that requires treatment whereas a much greater percentage have sub-clinical compensated hypothyroidism with normal T4 and T3 but high TSH levels. [21]

No significant difference found in terms of mean age, sex, weight, height, WAZ score, HAZ score between euthyroid and hypothyroid cases. There was no significant difference in terms of age at first diagnosis (months), total duration of disease

(years), age at first blood transfusion (months), number of cases received iron chelation therapy, duration of iron chelation therapy in months and number of cases with good compliance to iron chelation therapy between the two groups. Hypothyroid patients received significantly greater number of blood transfusions than euthyroid patients ($p<0.0001$). The mean ferritin level was higher in hypothyroid group than in euthyroid group but p value was not significant. Mean FT4 and TSH values were significantly different in euthyroid and hypothyroid groups ($p\leq0.0001$). This finding was consistent with the study done by Hantrakool [22] as they suggested elevated serum ferritin level is a predictor of the development of hypothyroidism in thalassemia patients with iron overload and the maximum serum ferritin levels of greater than 3,500 ng/ml are associated with hypothyroidism in their study. These findings may necessitate the value of iron chelating therapy to maintain serum ferritin levels below 2000 ng/ml and this may delay or avoid the development of hypothyroidism in patients with thalassemia. Sanctis et al [23] suggested that Thyroid dysfunction usually starts in the second decade, and increases gradually in the third and fourth decades of life in patients who started early chelation therapy. In patients starting late iron chelation therapy, or with poor compliance to treatment, dysfunction of thyroid starts earlier. Therefore, an assessment of thyroid function is generally recommended after the age of 10 years.

Conclusion

In the present study we documented hypothyroidism in transfusion dependent thalassemic children. Among them majority were compensated hypothyroidism. Higher number of blood transfusion and ferritin level ≥2000 ng/ml was found significantly associated with the development of hypothyroidism in thalassemic patients.

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