

## Frequency of Hypothyroidism in Patients with Beta-Thalassemia Major

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### ABSTRACT

**Objective:** To determine the frequency of hypothyroidism in patients with beta-thalassemia major in Paediatric department of Pak Emirates Military Hospital, Rawalpindi Pakistan.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Paediatric Medicine Department, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Nov 2018 to Oct 2019.

**Methodology:** All transfusion dependant beta-thalassemia major (BTM) patient sir respective of age and gender were consecutively enrolled. For the assessment of thyroid function, a random sample of 3 ml venous blood was drawn. The presence of increased thyroid stimulating hormone and normal T4, T3 were labelled as compensated, increased thyroid stimulating hormone, decreased T4 and/or T3 as uncompensated.

**Results:** Of 73 patients, the mean age of the patients was  $7.0 \pm 3.87$  years. All the patients were getting iron chelation therapy. The mean serum ferritin level was  $3911.68 \pm 2017.36$  ng/mL. Twenty-eight (38.4%) cases were hypothyroid. Subclinical hypothyroidism was documented in 25(89.3%) while clinical hypothyroidism in 3(10.7%) patients. Patients with age  $>8$  years ( $p < 0.001$ ),  $>2$  years of age at the time of 1st blood transfusion ( $p < 0.001$ )  $>8$  numbers of blood transfusion ( $p < 0.001$ ) and  $>4000$ ng/dl serum ferritin levels ( $p < 0.007$ ) were noted as factors significantly associated with hypothyroidism.

**Conclusion:** A considerable number of patients were affected with hypothyroidism. Moreover, high serum ferritin level and a high number of blood transfusions were found to be significant determinants.

**Keywords:** Beta-thalassemia major, Hypothyroidism, Serum ferritin level.

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## INTRODUCTION

Thalassemia is a genetically transmitted autosomal recessive blood disease which results in a quantitative defect in the production of beta chain of haemoglobin. This defect results in an imbalance between alpha and beta-globin chains (that combine to form adult haemoglobin) consequently causing hemolysis and hence anemia.<sup>1,2</sup>

In Pakistan, with a population of more than 200 million, yearly approximately 9000  $\beta$ -thalassemia major (BTM) children are born and around 40,000 are registered.<sup>3</sup> The projected carrier frequency in the overall population is 5-7%, which translates into 9.8 million carriers.<sup>4</sup>

Patients with BTM face multiple problems including hypothyroidism. It is a condition in which there is not enough thyroid hormone produced by the thyroid gland. Since the main purpose of thyroid hormone is to run the metabolism of the body, it is common to have symptoms associated with a slow metabolism in people with this condition. The most common type of

thyroid dysfunction in thalassemias is primary hypothyroidism that results due to iron deposition in the thyroid gland secondary to blood transfusion, leading to thyroid gland dysfunction. Depending on the place and quality of iron chelation practised, the hypothyroidism frequency may differ from 6-30%.<sup>5</sup> The primary hypothyroidism is split into sub-clinical hypothyroidism, which is characterized by high TSH with standard free T4, and high TSH with low free T4. In thalassemic cases prior to adulthood, low T4 and low TSH, the secondary or central hypothyroidism is rare.<sup>3,6</sup>

It is reported that clinical hypothyroidism in thalassemic patients has slowed-up development, retarded puberty, cardiac failure and pericardial effusion.<sup>6</sup> Good iron-chelation treatment and compliance can prevent sub-clinical hypothyroidism. This study was conducted to assess the hypothyroidism in patients with BTM.

## METHODOLOGY

The cross-sectional study was conducted at the Paediatric Department of Pak Emirates Military Hospital, Rawalpindi Pakistan from Nov 2018 to Oct 2019.

**Inclusion Criteria:** All transfusion dependant beta-thalassemia major (BTM) patients irrespective of age

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and gender were enrolled through non-probability consecutive sampling with informed consent.

**Exclusion Criteria:** Patients having acute infection at the time of study or having history of splenectomy were excluded.

Ethical approval was obtained from the Pak Emirates Military Hospital, Rawalpindi (Ltr no. A/28/EC/54/19). Epi Info sample size calculator was used for the estimation of sample size taking confidence interval 95%, a margin of error 10%, reported prevalence of hypothyroidism in beta-thalassemia major patients 25.7%.<sup>7</sup> The final sample size came out to be 73.

For the assessment of thyroid function, a random sample of 3ml venous blood was collected with informed consent. The blood sample was drawn approximately 2 weeks post blood transfusion. Serum samples were analyzed after ultracentrifugation. Thyroxine (T4) triiodothyronine (T3), & thyrotropin (TSH) were evaluated via enzyme-linked immunosorbent assay (ELISA).

TSH level of >4 µIU/ml, T4 levels <4.5 µg/dl and T3 levels <82ng/dl was defined as hypothyroidism. The presence of increased TSH and normal T4, T3 were labelled as compensated, increased TSH, decreased T4 and/or T3 as uncompensated, whereas normal TSH and normal free T4 as euthyroidism. This information along with demographic characteristics like age, gender, age at the time of 1st transfusion, number of transfusions, and serum ferritin levels were noted in a pre-designed proforma.

Statistical analysis for social sciences (SPSS) version 22 was used for data analysis. Quantitative variables like age, age at the time of 1st blood transfusion, number of transfusions per year, duration of blood transfusion, and serum ferritin level were explored using mean and standard deviation. Frequency and percentages were calculated for gender and the presence of hypothyroidism. Inferential statistics were explored using chi-square test and independent t-test. *p*-value ≤0.05 was taken as significant.

**RESULTS**

Of these 73 patients with beta-thalassemia major, the mean age was 7.0 ±3.87 years. There were 42 (57.5%) males and 31(42.5%) females. The mean age at the time of 1st blood transfusion was 3.74±2.91 years, the mean number of transfusions was 10.22±8.29 per year, whereas the mean duration of blood therapy was 4.32±3.40 years. All the patients were on iron chelation therapy. The mean serum ferritin level was 3911.68±2017.36 ng/mL. Twenty-eight (38.4%) patients had

hypothyroidism. Of these patients with hypothyroidism, subclinical hypothyroidism was observed in 25(89.3%) while clinical hypothyroidism was observed in 3(10.7%) patients.

The mean age (*p*<0.001), age at the time of 1st blood transfusion (*p*<0.001), transfusion numbers (*p*<0.001), and serum ferritin levels (*p*=0.007) were noted as factors significantly associated with hypothyroidism. (Table-I and Table-II)

**Table-I: Comparison of Hypothyroidism with baseline Characteristics of the patients (n=73)**

Variables	Hypothyroidism		p-value
	Yes	No	
Age, years	n (%)	n (%)	
≤8	16(29.6)	38(70.4)	0.001
>8	12(63.2)	7(36.8)	
<b>Gender</b>			
Male	17(40.5)	25(59.5)	0.605
Female	11(35.5)	20(64.5)	
<b>Age at the time of 1st blood transfusion, years</b>			
≤2	7(18.4)	31(81.6)	<0.001
>2	21(60.0)	14(40.0)	
<b>Number of transfusions per year</b>			
≤8	6(16.7)	30(83.3)	<0.001
>8	22(59.5)	15(40.5)	
<b>Duration of blood transfusion, years</b>			
≤3	19(48.7)	20(51.3)	0.051
>3	9(26.5)	25(73.5)	
<b>Serum Ferritin level, ng/mL</b>			
≤4000	7(21.2)	26(78.8)	0.006
>4000	21(52.5)	19(47.5)	

Chi-square test applied, *p*-value <0.05 taken as significant

**Table-II: Mean difference of Baseline Characteristics with respect to Hypothyroidism (n=73)**

	Hypothyroidism		p-value
	Yes	No	
	n=28	n=45	
Age, years	8.96±3.50	6.39±3.81	0.005
Age at the time of 1st blood transfusion, years	5.54±3.67	2.62±1.49	<0.001
Number of transfusions per year	16.42±8.81	6.36±5.01	<0.001
Duration of blood transfusion, years	3.64±3.21	4.73±3.49	0.181
Serum Ferritin level, ng/mL	4608.61±1785.37	3478.61±2049.91	0.019

**DISCUSSION**

The finding of this study has reported relatively higher serum ferritin level in patients with BTM.

However, as most of the patients with BTM belonged to low-socioeconomic status and iron chelation medications are expensive and is administered life long, low compliance with iron chelation therapy was noticed.

In BTM due to an imbalance, there becomes an excess of free alpha-globin genes that start to precipitate as they find no beta-globin chain to bind. Presence of these precipitates damages the cell membrane of the Red Blood Cells (RBCs) that result in hemolysis. Resulting Anemia and consequent hypoxia stimulates the kidney to increase erythropoietin production but as erythropoiesis is ineffective due to defect in genes, continuous positive feedback mechanism consequently leads to bone marrow expansion. This expansion in bone marrows is reflected in the skeletal changes seen in thalassemia patients. This calls for the immediate need for the blood transfusion.<sup>8</sup> Though blood transfusions are required to save their lives, however, it results in iron overload. Every administered unit of Packed cell (500 ml) contains 250 mg of iron. With frequent and multiple transfusions, iron continuously gets overloaded in the body of the patients affecting their various organs including heart, liver and endocrine glands. Cardiac death, liver cirrhosis, endocrine abnormalities including failure of growth, delayed or absent puberty, diabetes mellitus, hypothyroidism and hypoparathyroidism consequently occur due to iron overload.<sup>9-11</sup>

A considerable number of patients with hypothyroidism was found in this study. Somewhat similar findings were observed in a study by Malik *et al.* in which around twenty-six percent BTM patients had hypothyroidism.<sup>7</sup> Similarly, serum ferritin level was also found significantly higher in the study of Malik *et al.*<sup>7</sup> In a recent study, Saleem *et al.* reported hypothyroidism in around thirty-one percent patients. The estimates of international studies have reported hypothyroidism in BTM range from 7-26% whereas the prevalence of hypothyroidism in national studies are found to be somewhat higher and ranged from 25-31%.<sup>12</sup>

In our study, among BTM patients with hypothyroidism, the majority of them had subclinical hypothyroidism. While clinical hypothyroidism was documented in only three patients. These findings were consistent with a previous study conducted by Saleem *et al.* in 2016, in which clinical hypothyroidism was found in 3 patients only.<sup>12</sup>

In addition to this, a significant association of hypothyroidism in BTM patients was also observed

with age, age at the time of first blood transfusion, and the number of transfusions.

BTM patients who died young previously have now survived enough time to seek medical attention with the gradual improvement in health care services. In developing countries like Pakistan, this poses an increasing burden for health-care services besides increasing suffering for an individual and families.<sup>13-15</sup> Monthly blood transfusions accompanied by iron-chelation therapy are required for the survival of the affected children.<sup>16-18</sup>

The findings of this study could be highlighted in light of the limitation that this study was a descriptive study conducted in a single-centre hospital. Further, large scale multi-centre longitudinal studies are recommended to monitor the consequences of iron overload in BTM patients. One more prevalent issue is that the clinician fails to acknowledge this or to adjust the dose downwards enough to avoid toxicity of over chelation in patients who react well to a chelation therapy. This maladministration is more prevalent at health centres, where iron chelation is not long-standing or regularly monitored. The minimum demands are regular monitoring and management of abnormal serum ferritin trends, and recognized toxicities of each chelator.<sup>19,20</sup>

### CONCLUSION

Hypothyroidism especially subclinical is quite common in BTM cases. It is recommended to monitor these children for hypothyroidism on regular basis. Better compliance to iron chelation can reduce hypothyroidism.

**Conflict of Interest:** None.

### Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SJ & TG: Study design, drafting the manuscript, concept, critical review, approval of the final version to be published.

SH & FI & RN: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors 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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