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STUDY THE THYROID DYSFUNCTION IN MULTIPLE BLOOD TRANSFUSED CHILDREN WITH BETA-THALASSEMIA MAJOR AND FIND OUT EFFECT ON THEIR GROWTH

Paediatrics

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ABSTRACT

Detection of hypothyroidism in multiple transfused children with β-thalassemia is of great clinical significance. Hypothyroidism can itself cause growth failure, which can add to the existing growth retardation in thalassemia patients. The aim of this study was to evaluate thyroid function status in β-thalassemia major patients and effect on their growth.

METHOD: This study included 105 children diagnosed with beta-thalassemia major admitted for blood transfusion and chelation therapy. It was a hospital based cross-sectional study included multiple blood transfused children (≥20) aged 1 to 18 years of both sexes (M: F ratio 2:1). Patients were subjected to a detailed history and physical examination to evaluate the demographic information, quality of their last transfusions, chelation therapy and growth parameters. We assessed serum T4, TSH, serum ferritin in all patients.

RESULT: Out of 105 cases, 18(17.1%) were diagnosed with hypothyroidism in which 14(13.3%) had sub-clinical hypothyroidism (normal T4 levels with a raised TSH values) and 4 (3.8%) had central hypothyroidism (T4 level were low and TSH was normal or low). Subclinical hypothyroidism was more common in the present study. 51 (48.6 %) cases were short stature. Short stature is more in female (60%) as compared to male (42.9%). Correlation between thyroid dysfunctions and height (< 3rd percentile) for age were statistically significant (p value 0.01). Correlation between thyroid dysfunction and weight for age was statistically significant (p value 0.04).

CONCLUSION: High prevalence of hypothyroidism among β-thalassemia patients signifies the importance of regular screening for evaluation of endocrine function in these patients; especially when short stature is present.

KEYWORDS

β-thalassemia major, Growth retardation, Hypothyroidism, Multiple blood transfusion, Serum ferritin.

INTRODUCTION

Thalassemia is a major health problem, placing an immeasurable emotional, psychological and economic burden on millions of people around the world. Thalassemia is a recessively inherited blood disorder passed down through families in which the body makes an abnormal form of haemoglobin. β-thalassemia is characterized by deficient synthesis of the beta globin chain. Thalassemia is the most common monogenic disorders in the world. Blood transfusion is the mainstay of the care of individuals with thalassemia major. The purpose of transfusion is twofold; to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth failure, skeletal and neurological complications of thalassemia major. Treatment with a regular transfusion program, chelation therapy, bone marrow transplantation and medication aimed at reducing transfusion iron overload, allows for normal growth and development and extends life expectancy. As per WHO estimates, 4.5% of the World's population is carriers of hemoglobinopathies and thalassemia is the commonest of them. The overall prevalence of β-thalassemia in India is 3-4%.[1] Iron overload is a common complication of thalassemia syndrome which could lead per se to the development of organ damage and increased mortality. Patient with iron overload demonstrate signs of endocrinopathy caused by iron deposits including the hypothalamico-pituitary thyroid axis which includes thyroid dysfunctions. Thyroid dysfunctions mainly occur by gland infiltration, chronic tissue hypoxia, free radical injury and organ hemosiderosis. Presence of hypothyroidism had been documented in a number of studies; which is mainly subclinical in nature.[2,3] Detection of hypothyroidism is of great clinical significance. Hypothyroidism can itself cause growth failure, which can add to the existing growth retardation in thalassemia patients. Subclinical hypothyroidism requires only careful follow up. Thyroxine replacement can halt the growth retardation caused by hypothyroidism.

MATERIAL AND METHOD

This study was conducted in Department of Pediatrics, JLN Medical College and Associated Group of Hospitals, Ajmer from July 2018 to June 2019. Includes 105 children from 1 to 18 years of age of both sexes diagnosed with beta-thalassemia major admitted in the Department of Pediatrics, only those who had received 20 or more (PCV) Blood Transfusion were selected for the study. Thalassemia patient not receiving blood transfusion therapy, patients with other haemoglobinopathies including α thalassemia, beta thalassemia trait, having severe anemia and patients with family history of hypothyroidism were excluded. All the selected 105 children were subjected to detailed clinical evaluation including detailed history, general and systemic examination with special emphasis on blood transfusion and concomitant iron chelating therapy.Growth was measured by height (cm) and weight (kg) and accessed by using Growth charts of the WHO Child Growth Standards.[4] Blood samples were taken for CBC, TLC, Hb, serum ferritin, thyroid function tests (TSH, Total T4). Hemoglobin was estimated on the same day by Automated Analyzer from the EDTA sample. Thyroid function tests (Total T4 and TSH) and Serum ferritin level were performed by using ELISA technique. Hypothyroidism was defined as TSH level >5.5μIU/ml, Total T4 levels <6.8μg/dl in 1 to 3year, <5.5μg/dl in 3 to 10 year and <4.2μg/dl in >10year children. Collected data were statistically analyzed. Significance of difference in mean ± SD was expressed using 'unpaired T' test. Values of p <0.05 were considered statistically significant.

RESULTS

In the present study comprising 105 children diagnosed with β-thalassemia major 70 (66.6%) were male and 35 (33.3%) were female (ratio 2:1).

Out of total 105 cases, thyroid function tests were abnormal in 18 children; 14 (13.3%) cases had Subclinical hypothyroidism (had normal T4 levels with a raised TSH values), central hypothyroidism was present in 4 (3.8%) cases (T4 level were low and TSH was normal or low) and 87 (82.9%) had normal thyroid function, primary hypothyroidism was not present in any case (low T4 associated with raised TSH) (TABLE 1). Central hypothyroidism was present only in males in our study. According to the thyroid hormone function tests patients were classified in appropriate category based only on the laboratory values of thyroid function tests; we did not consider clinical manifestations of the hypothyroidism.

Table 1: Classification Of Hypothyroidism On The Basis Of Laboratory Reports

S. No.	Type of Hypothyroidism	Laboratory criteria	No. of cases
1.	Subclinical hypothyroidism	Raised TSH, normal T4	14
2.	Overt hypothyroidism	Raised TSH, low T4	0
3.	Primary hypothyroidism	Raised TSH, low T4	0
4.	Central hypothyroidism	Low or normal TSH, low T4	4

Among all patients with normal thyroid function 25(43.4%) male and 16(53.3%) female were short stature. 3(33.3%) out of 9 male and all 5(100%) females with subclinical hypothyroidism were short stature. 2(50%) out of 4 male children with central hypothyroidism were short stature (TABLE 2). Thyroid dysfunctions and height for age (<3rd percentile) of thalassemia major children correlated and was statistically significant (p value 0.01).

Table 2: Association Between Thyroid Dysfunction And Height For Age Percentile

Height for age	Thyroid dysfunctions						
	Normal		Subclinical hypothyroidism		Central hypothyroidism		Total No.=105
	Male	Female	Male	Female	Male	Female	
<3rd percentile	25 (43.4%)	16 (53.3%)	3 (33.3%)	5 (100%)	2 (50%)	0	51
>3rd percentile	32 (56.1%)	14 (46.7%)	6 (66.7%)	0 (0%)	2 (50%)	0	54
Total	57 (65.5%)	30 (34.5%)	9 (64.3%)	5 (35.7%)	4 (100%)	0	105
P value	0.4	0.78	--				
Total	87	14	4	105			

P value=0.01 (S).

Among all patients with normal thyroid function 22(38.5%) male and 15(50%) female were underweight. Patients with subclinical hypothyroidism 2(40%) out of 5 females were underweight and patients with central hypothyroidism 1(25%) out of 4 males were underweight (TABLE 3). Thyroid dysfunctions and weight for age (<3rd percentile) of thalassemia major children correlation was statistically significant (p value 0.04)

Table 3: Association Between Thyroid Dysfunction And Weight For Age Percentile

Weight for age	Thyroid dysfunctions						
	Normal		Subclinical hypothyroidism		Central hypothyroidism		Total No.=105
	Male	Female	Male	Female	Male	Female	
<3rd percentile	22 (38.5%)	15 (50%)	0	2 (40%)	1 (25%)	0	40
>3rd percentile	35 (61.6%)	15 (50%)	9 (100%)	3 (60%)	3 (75%)	0	65
Total	57 (65.5%)	30 (34.4%)	9 (64.2%)	5 (35.7%)	4 (100%)	0	105
P value	0.3	0.48	--				
Total	87	14	4	105			

P value=0.04 (S)

DISCUSSION

Our study included total 105 subjects with confirmed diagnosis of β-thalassemia major from the age group of 1 to 18 years with male and female ratio 2:1. The preponderance of males could be due to males being paid better care and attention. The mean age of patients with hypothyroidism was lower than reported in other studies, which may be due to inadequate chelation therapy, chronic anemia and malnutrition that is commoner in this part of the world.[5]

18 (17.1%) patients diagnosed with hypothyroidism, from which 14 (13.33%) patients had subclinical hypothyroidism, overt hypothyroidism/primary hypothyroidism was not present while central hypothyroidism was present in 4 (3.8%) patients. In the study done by *Athanasios Zervas et al*[6], a milder form of 'biochemical' thyroid dysfunction (subclinical hypothyroidism) was found to be more prevalent (12.5%) than overt hypofunction (4%). In the study of *Peiman Eshragi et* al[7], hypothyroidism was present in 19 patients (14.6%); 2 primary overt hypo-thyroidism,3 secondary hypothyroidism and 14 subclinical hypothyroidism cases were detected.

51 (48.6%) cases were below 3rd percentile for height according to age. In our study it was statistically significance, with more height retardation in females as compared to males (P value =0.03). *Soliman et al*[8] reported a prevalence of short stature (<2SD) in 49% of their thalassemic patients. *Moayeri et al*[9] showed that 62% were less than 2SD and 49% were 3SD below the mean and also confirmed decreased growth hormone response to two provocative tests and low levels of IGF-1in a majority of their thalassemic patients. Within 14 patients diagnosed with subclinical hypothyroidism 8 (57.1%) were short stature in which 3 (33.3%) out of 9 male and 5 (100%) out of 5 females. Within 4 male patients diagnosed with central hypothyroidism 2(50%) were short stature. whereas out of 87 patients with normal thyroid function 41 (47.1%) were short stature with 25 (43.4%) males out of total 57 and 16 (53.3%) females out of total 30. The retardation in height was slightly more in cases with hypothyroidism. Female patients had 100% height retardation with subclinical hypothyroidism. In our study the correlation between thyroid dysfunction and height retardation was significant statistically (P value =0.01). So, it can be said from this study, that growth retardation seen in thalassemia patients and correlated with hypothyroidism was statistically significant. *Pignetti et al*[10] showed where they found statistical significance between height and thyroid dysfunction, with 37% of thalassemia cases below two standard deviation from mean in height & weight in a group of 250 patients.

40 (38.1%) cases were below 3rd percentile for weight according to age. Females are more underweight as compared to males. The correlation between thalassemia patients and weight retardation was statistically significant (P value=0.01). Out of 14 patients with subclinical hypothyroidism 2(14.3%) were underweight and within 4 patients with central hypothyroidism 1(25%) were underweight whereas out of 87 thalassemia patients with normal thyroid function 37(42.5%) were underweight. This shows that, thalassemic with subclinical and central hypothyroidism along with pituitary involvement were less retarded in weight when compared with cases with normal thyroid function. This needs further evaluation. The comparison between weight retardation and hypothyroidism was statistically significant (P value 0.04). Potential causative factors for growth failure include iron overload, free radical toxicity, desferrioxamine toxicity, zinc deficiency, anemia, delayed puberty, primary hypothyroidism, liver cirrhosis and defect in the Growth Hormone-Insulin- like Growth Factor-1 axis.[11]

Correlation between serum ferritin level and thyroid hormone dysfunction was not statistically significant in our study. There is no doubt that iron overload has important role to play in thyroid and other endocrinal dysfunction in thalassemic patients, non-significant difference in ferritin levels between hypothyroid and euthyroid group suggests that there is other mechanism by which thyroid dysfunction occurs in these children. It also suggests that recent ferritin levels are not a sensitive marker for tissue ferritin deposition. *Peiman Eshragi et al*[7] studied that the absence of the relationship between ferritin and hypothyroidism may be explained by suggesting that the damage of endocrine glands caused by chronic ischemia is more pronounced than that caused by hemosiderosis as a consequence of iron overload. They found that correlation between hypothyroidism and serum ferritin level was not significant (p=0.584).

CONCLUSION

It concludes that growth retardation was common problem in our patients, with significant relevance of physical growth and hypothyroidism ,subclinical hypothyroidism was commonest thyroid dysfunction, no relation with serum ferritin but related to NBT significantly, warranted regular assessment of thyroid function, intensive chelation therapy , with growth parameters monitoring , nutritional supplementation and diet charts with follow up and genetic counselling necessary for minimizing complication .

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