A study of thyroid function in children with Beta thalassemia major.

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Abstract:

One of the most common endocrine disorder in beta-thalassemia major is Hypothyroidism. The aim of this study was to evaluate thyroid function status in β-thalassemia major patients above the age of 7 years. ***Materials & Methods:*** This cross sectional study was carried out on beta thalassemia major patients registered at Thalassemia Centre of civil hospital, Ahmedabad. A questionnaire was filled out to evaluate the demographic information, information about transfusions and chelation therapy. Growth parameters were evaluated. We assessed serum fT_4, fT_3 and TSH levels in all patients above 7 years with consent and those who were found to have hypothyroidism were subjected to further management. ***Results:*** 97 patients (7-14 years age) (46 males and 51 females) were enrolled in this study. Hypothyroidism was found in 18 patients (15.3%); 5 patients with primary overt Hypothyroidism, and 13 patients with subclinical primary Hypothyroidism were detected. Out of 18patients, 8 patients were male and 10 patients were female.11 patients were above 11 year of age and 6 patients between 9-11 year of age and 1 patient below 9 year. Short stature was found in 62(63.9%) patients. Correlation of Hypothyroidism with serum ferritin level and short stature was significant. Regular transfusion and chelation therapy were associated with ferritin level. ***Conclusion:*** High prevalence of Hypothyroidism among thalassemia patients signifies the importance of regular screening for evaluation of endocrine function in these patients, especially after 7 year of age and when ferritin levels are high.

Key Words: Beta- thalassemia major, Hypothyroidism, Serum ferritin.

Introduction:

Beta (β)-thalassemia is a genetic disorder of beta globin gene. In β-thalassemia major patients, β-globin proteins are not enough (β^+) or do not exist (β^0). More than 200 mutations can cause β-thalassemia but 20 incident alleles bring 80% of thalassemia in the world.[1] The combination of transfusion and chelation therapy has dramatically extended the life expectancy of thalassemia patients who can now survive into their fourth and fifth decades of life.[2] However, frequent blood transfusion in turn can result in iron overload which may lead to various complications.[3] Thalassemia's complications can be a result of many mechanisms. Most complications are caused by increased iron deposition in tissues like heart, endocrine glands and these result in heart failure, arrhythmia, hypothyroidism, diabetes mellitus and so on.

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Decrease in production of thyroid hormones according to body demand or defect in thyroid hormone receptors cause hypothyroidism. In several studies, hypothyroidism has been reported to be associated with low serum ferritin level. Thyroid dysfunctions are well documented in patients with thalassemia major requiring frequent and recurrent blood transfusion. Also, growth retardation is another complication that usually occurs. Although many studies report endocrinopathy in thalassemia patients, results are controversial and different, according to genetic and geographic characteristics and ferritin level, thus we decided to evaluate thyroid function in patients of beta thalassemia major at our institute and correlate the findings with short stature, regular transfusion, chelation therapy and serum ferritin level in these patients.

Materials & Methods:

This cross-sectional study was carried out on 97 patients above age of 7 years, attending the thalassemia clinic at civil hospital Ahmedabad from June 2017 to march 2018. Patients who agreed to participate in the study, filled a consent for same and completed a questionnaire consisting of demographic information, age of disease onset, frequency of transfusions and its interval time, dose of deferasirox, serum ferritin level, history of endocrine problems and referral to endocrinology clinic. Serum ferritin was measured and patients with serum ferritin lower than 3000ng/ml were categorized in well controlled group. Patients with serum ferritin more than 3000 ng/ml were categorized in poorly controlled group. Patients with ferritin level >1000 ng/ml were treated with iron chelators such as deferasirox.

We measured serum level of freeT_3 (trithyroiodine), TSH (thyroid stimulating hormone), freeT_4 (thyroxin) and ferritin. Normal range and methods are mentioned in Table 1

Table 1: Normal range of Tests

Test	Normal-range	Unit
Free T_3	2.1-4.4	pg/ml
Free T_4	0.8-2.7	ng/dl
TSH	0.4-4	µIU/ml
Ferritin	20-250	ng/ml

We categorized hypothyroidism in three sets:

1) Primary overt hypothyroidism: low FT_3, TSH>15 µIU/ml;
2) Secondary hypothyroidism: low FT_3, low TSH response;
3) Subclinical primary hypothyroidism: normal FT_3, TSH: 4-15 µIU/ml[4]

According to patients' data, relation between hypothyroidism with short stature, ferritin level and compliance in blood transfusion and chelation therapy was evaluated.

Analysis was performed by Student's t-test, the Mann-Whitney and λ^2 test were used for analysis. $p<0.05$ was considered statistically significant.

Results:

97patients (7-14 years age) (46 males and 51 females) were enrolled in this study.

Hypothyroidism was detected in 18 patients (15.3%); 5 patients with primary overt Hypothyroidism, and 13 patients with subclinical primary Hypothyroidism were detected. Short stature (height <3rdpercentile) was detected in 35 patients (36%):19(37%) female patients and 16(34%) male patients. The mean serum ferritin of study group was 3735 ± 756 ng/ml (3748 ± 744 ng/ml in female patients and 3724±762 ng/ml in male patients). 39(40.2%) patients belonged to well controlled group of chelation therapy (ferritin<3000). In 12 patients, serum ferritin was >5000µg/L.

Image 1 Type of hypothyroidism

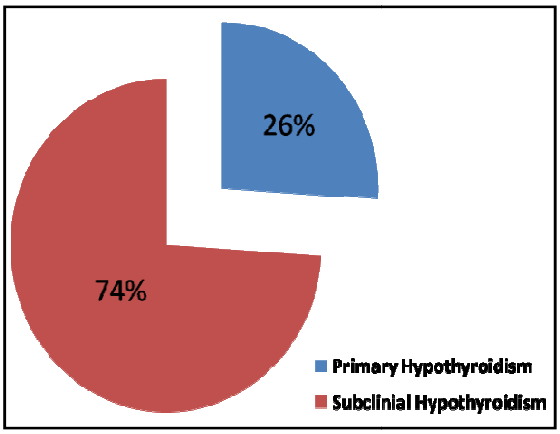


Image 2 Association between thalassemia, Short stature and hypothyroidism

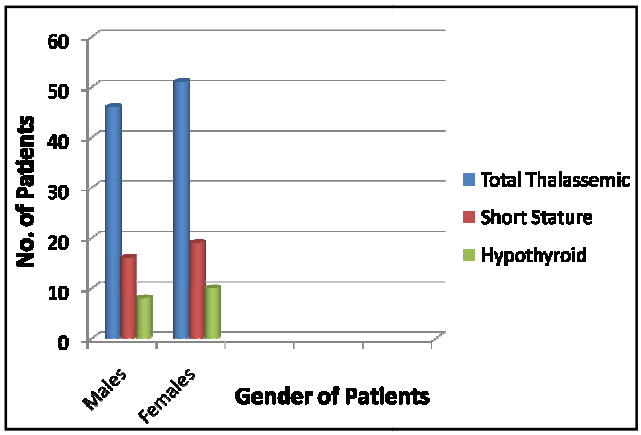
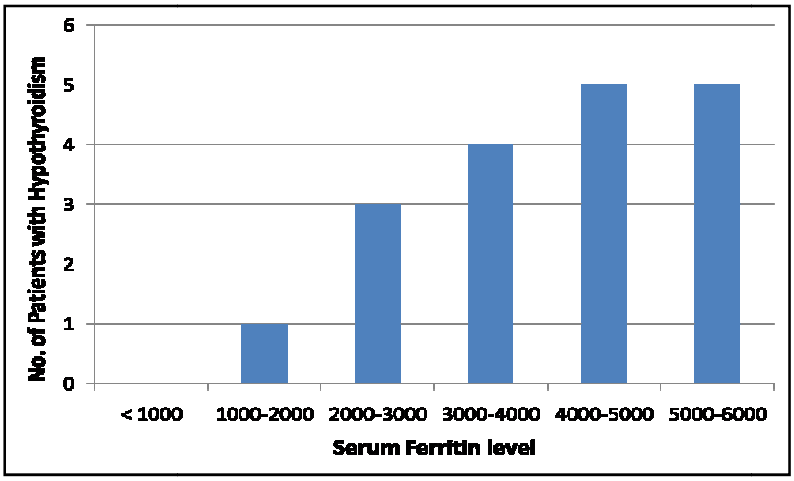


Table 2: Age and Sex wise Distribution of Hypothyroidism:-

Gender	7-9 years	9-11 years	11-14 years	Total
Male	0	3	5	8
Female	1	4	5	10

Image 3 Correlation between hypothyroidism & serum ferritin in thalassemia patients.



It was observed that there was a significant relationship between serum ferritin and hypothyroidism. High ferritin level was associated with higher incidence of hypothyroidism. Mean serum TSH of study group was about 4.40±4.68 µIU/ml. 18 patients had excess TSH value (>4µIU/ml). Primary Overt Hypothyroidism was detected in 5 patients and subclinical primary hypothyroidism was detected in 13 patients. There was no association in Hypothyroidism and patient's gender (p=0.36) but there was significant association between

ferritin level and the patient's compliance ($p<0.001$). Also, higher degree of short stature (height < -3SD) was associated with hypothyroidism ($p=0.002$).

Discussion:

Iron overload of tissue is the most important complication of beta-thalassemia and is a major subject of management. After approximately one year of transfusions, iron starts to be accumulated in parenchymal tissues. Hypothyroidism is related to the accumulation of iron in thyroid gland due to frequent blood transfusions and iron overload leading to thyroid gland dysfunction. Short stature is one of the most prevalent complication in thalassemia. Those with Hypothyroidism have higher degree of stunting. We studied 97 patients with beta thalassemia major from which 18 cases suffered from hypothyroidism (18.6%). De Sanctis reported 25.6% incidence of hypothyroidism in Italy.[5,6] Another study in Iran reported 14.6% incidence of hypothyroidism.[7] The difference in results may be because of genetic, geographic, cultural, economical factors and also regularity of blood transfusion and chelation therapy.

Mean serum ferritin level was 3735±756ng/ml and there was no significant difference between the males and the females. 12% of patients' serum ferritin was more than 5000 ng/ml.

The relationship between ferritin and Hypothyroidism may be explained by suggesting that the damage of endocrine glands is caused by hemosiderosis as a consequence of iron overload.

For patients who were diagnosed with hypothyroidism, Endocrinologist opinion was taken and treatment was started according to protocol. For patients with subclinical hypothyroidism also endocrionologist opinion was taken, serial measurement of thyroid function and regular follow-up was done and treatment was given as and when required.

Conclusion:

From our study, we found that in paediatric patients of thalassemia, there is increased incidence of hypothyroidism as ferritin level increases and hypothyroidism further increases the degree of short stature in patients of thalassemia. So regular screening of thyroid function should be done for thalassemia patients for early detection and management of hypothyroidism.

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