THYROID DYSFUNCTION IN THALASSEMIA MAJOR PATIENTS

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ABSTRACT

BACKGROUND AND AIM- Thalassemia is one of the major hemoglobinopathies in India, requiring multiple blood transfusion. These patients have iron overloads and related end-organ damage irrespective of transfusion requirements as they have increased iron absorbing capacity. India tops the list with largest number of children with Thalassemia major in the world – about 1 to 1.5 lakhs and almost 42 million carriers of ß (beta) thalassemia trait. The main aim of this study is to determine the prevalence of thyroid disorder in multi transfused thalassemia major patients and to detect thyroid disorder at earlier stage so that prompt management can be initiated for better quality of life and to reduce thyroid disorder related morbidity.

MATERIAL AND METHODS- The study included thalassemia major patients above the age of 12 years. Patient‘s serum ferritin level measured for the evaluation of iron status and thyroid stimulating hormone(serum TSH), T4, T3 for thyroid function status.

RESULT- Out of 100 patients included in the study, there were 61 male patients; the mean age was 22 years(range: 12-34 years). The prevalence of hypothyroidism in our study was 14(14%) patients of which 5(5%) patients had overt hypothyroidism with mean ferritin level of 4738 ng/ml and 9(9%) patients had Subclinical hypothyroidism with mean ferritin level of 5595 ng/ml. 86(86%) patients showed normal thyroid function with mean ferritin level of 2934 ng/ml.

CONCLUSION- Thalassemia major patients had higher prevalence of hypothyroidism than the general population but the serum ferritin level did not correlate with thyroid dysfunction.

Keywords- beta thalassemia major, thyroid dysfunction, TSH, iron overload, iron chelation

INTRODUCTION

Thalassemia is one of the most common genetic disorder in the world[1]. Beta thalassemia syndromes are inherited disorders which are characterized by deficiency in the production of beta globin chains resulting in ineffective erythropoiesis. Blood transfusions and iron chelation therapy are standard treatment for patients affected by beta thalassaemia major(BTM). BTM patients requiring multiple blood transfusion may develop severe endocrine complications due to iron overload[2]. Moreover, despite their initial transfusion-independence, BTM patients can still accumulate iron due to increased intestinal absorption[3].

The average prevalence of beta thalassemia carriers is 3-4% which translates to 35 to 45 million carriers in our multi-ethnic and culturally and linguistically diverse population of 1.21 billion people, according to the Census of India 2011. Several ethnic groups have a much higher prevalence (4-17%)[4,5]

The study was undertaken to evaluate thyroid dysfunction in patients with BTM and it’s correlation with serum ferritin level.

MATERIALS AND METHODS

This prospective cross-sectional study was carried out on 100 patients older than 12 years suffering from BTM taking treatment from OPD & IPD of medicine department, PDU medical college and hospital, Rajkot. This study was done over a period of 1 year. The inclusion criteria for the study were age more than 12 years who required regular blood transfusion and were on iron chelation therapy and included only those who gave consent to participate in the current study. The exclusion criteria for the study were pregnancy, co-inheritance and other thalassemia and critically ill patients.

Detailed clinical history was taken regarding thalassemia and thyroid disorders as per established clinical studies along with the following investigations: complete blood counts, thyroid function test(TSH, T4, T3) and serum ferritin assay. Serum ferritin was measured and patients with serum ferritin lower than 1000 ng/ml

were categorized in good controlled group. Patients with serum ferritin more than 1000 ng/ml were categorized in poor controlled group. The below table-1 shows the normal range of TFT and serum ferritin.

BTM patients were categorized into 2 sets: 1. Primary overt hypothyroidism: low T4 and T3 with raised TSH levels (Serum TSH >4.5pg/ml); and 2. Primary Subclinical hypothyroidism: normal T4, and T3 with raised TSH levels (Serum TSH >4.5pg/ml).

STATISTICAL ANALYSIS

All recorded data were analysed using standard statistical method, and the findings were discussed in detail to draw an appropriate conclusion. Fischer's exact test was used for dichotomous variables. Statistical significance was assumed at a $P<0.05$ and $P<0.1$ was considered as highly significant. Linear regression was used to test correlation among variables TSH, T4, T3 with serum ferritin (figure 3)

RESULT

The study population of 100 patients consisted of 61(61%) boys and 39(39%) girls. Among them 45(45%) patients belonged to 2nd decade, 49(49%) patients belonged to 3rd decade and 6(6%) patients belonged to 4th decade of life (table 2). The prevalence of hypothyroidism in our study was 14(14%) patients of which 5(5%) patients had overt hypothyroidism with mean ferritin level of 4738 ng/ml, among them 4% patients belonged to 2nd decade and 1(1%) patient belonged to 3rd decade. 9(9%) patients had Subclinical hypothyroidism with mean ferritin level of 5595 ng/ml, among them 4(4%) patients belonged to 2nd decade 4(4%) patient belonged to 3rd decade and 1(1%) belonged to 4th decade. 86(86%) patients showed normal thyroid function with mean ferritin level of 2934 ng/ml.

DISCUSSION

Thalassemia is one of the most important genetic diseases and thyroid dysfunction is very well documented in these patients. BTM patient on regular transfusions and suboptimal chelation are at an increased risk for iron overload. Like in all organs, iron is deposited in the thyroid interstitium resulting in thyroid hemosiderosis[6] which slowly leads to worsening of the thyroid function. The study aims to evaluate the thyroid dysfunction in BTM patients who are on regular blood transfusion with iron chelation and it's correlation with Serum ferritin being an acute phase protein is also a product of hepatocellular damage and hence the elevated levels can be seen in conditions such as sepsis, hepatitis and congestive heart failure etc. No patients involved in our study had any clinical evidence of hepatitis or heart failure. There were many reports relating to the endocrine dysfunction with iron overload, it was recently demonstrated that the degree of iron overload, at least reflected by serum ferritin levels, was not associated with the development of endocrine complications[7,8].

We studied 100 BTM patients, 14% patients suffered from hypothyroidism as compared to 7% in Karamifar et al in Shiraz, 19% in piemanEshragi P et al , 16% in Najafpour et al in Tabriz, 7.7% Shamshiraz et al in Tehran, 21.6% in De Sanctus et al in Italy [9-13]. Variation in results may be due to many factors such as genetic, geographic, cultural, economical factors and also quality of blood transfusion and chelators.

Hypothyroidism was found to be a common form of thyroid dysfunction affecting 10.9% of the study population in India[14]. Compared to general population, there is increased prevalence of thyroid dysfunction in thalassemia patients[16].

In our study age cut off was 12 years and above. A study by Filosa et al[15] reported progressive increase of hypothyroidism increased over a period of 12 years to 13.9% by the age of 25.7 ±1.7 years. The prevalence of hypothyroidism was the highest in the age group of 46– 54 years (13.11%) and was lowest in that of 18–35 years (7.53%), in a study by Unnikrishnan et al[14], in the present study, we found thyroid dysfunction occurs at an earlier age in BTM patients compared to general population.

In the present study9% patients to had subclinical hypothyroidism compared to frank hypothyroid status(5%).Karamifar et al[11] from Iran found among beta-thalassemia intermedia patients have primary hypothyroidism in 21% of patients. Ghosh et al[17] from eastern India have found in their study subclinical hypothyroidism present in 23.52% of patients. The distinction between type of hypothyroidism and the thalassemia cohort differed from study to study.

In our study, analysis showed that there was no correlation with high mean serum ferritin levels and thyroid dysfunction, and the following studies also have similar results with varied number of patients. A study by

Mula-Abed et al[18] at Oman out of 30 BTM patients on regular blood transfusion, there was no significant difference (P > 0.050) in mean serum ferritin in patients with thalassemia with or without endocrinopathy, regardless of the number of endocrinopathy, however study by Malik et al[19] in homozygous beta thalassemia major showed frequency of hypothyroidism was associated with increased serum ferritin levels. A study by Zervas et al[16] out of 200 β thalassemia major patients, mean ferritin levels in hypothyroid and euthyroid patients were 2707.66 ±1990.5 μg/L and 2902.9 ±1997.3 μg/L, respectively, with (P = 0.61), indicating no correlation between ferritin levels and thyroid functional status.
In patients with thalassemia major and intermedia, iron deposition involves endocrine glands and hypothalamic-pituitary axis due to repeated blood transfusion and increased gastrointestinal absorption[20]. In developing countries, nonetheless, it is possible to have a high prevalence of endocrine complications at an early age due to multiple transfusions and suboptimal chelation therapy[16].
Thyroid function testing (TFT) in thalassemia patients are advised routinely, however, as per thalassemia international federation(TIF) guidelines, endocrine evaluation should be done based on whether the patient is on regular blood transfusion or not.If patient is not requiring blood transfusion[21], evaluation should be started at the age of 10 years; however if patient is requiring regular blood transfusion[22], there is no such specific age cutoff for TFT, but according to TIF guidelines, in BTM patients hypothyroidism should be suspected if there is stunted growth, delayed puberty, cardiac failure, and pericardial effusion.
Iron overload conditions are associated with many endocrinopathy in patients with thalassemia major and intermedia as depicted in the below table 4. Endocrine complications are commonly seen in both patients with thalassemia major and intermedia and necessitate close monitoring. Early recognition of these complications, institution of appropriate treatment including transfusion regimen and chelation therapy, and specific treatment of each complication are the keys to successful management[23].

Thyroid dysfunction in the form of subclinical and overt hypothyroidism in BTM patients had near about same ferritin level. Although iron overload is the major cause of endocrinopathy in BTM patients, iron overload is not the sole reason for thyroid dysfunction as other possible mechanisms such as iron-free radical-mediated damage to thyroid gland, chronic anemia and nutritional deficiency which needs to be studied further in future for definite answers.

CONCLUSION

The most common thyroid disorder in chronically transfused BTM children is subclinical hypothyroidism. In BTM patients there was no correlation found between thyroid dysfunction and factors like duration and amount of blood transfusions, serum ferritin level, and iron chelation therapy. Thyroid dysfunction was found in 14% of the study cohort but it was not statistically significant to establish a correlation between thyroid dysfunction and serum ferritin levels.

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