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Research Article

EVALUATION OF THYROID HORMONES IN B -THALASSEMIC CHILDREN OF NORTH INDIA

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ABSTRACT

Aim and objectives: β -thalassemia arises from a defect in the β globulin chain synthesis from clinically silent heterogeneous thalassemia minor to severe transfusion dependent thalassemia major. Transfusion related iron overload is the primary therapeutic complication in β -thalassemia major which leads to peroxidative stress and adversely affects the functioning of multiple organs. Hypothalamic–pituitary –thyroid axis, para-thyroid, adrenal, pancreas, gonads, all may show hypo-activity. The prognosis depends on the amount and the duration of iron overload. Therefore the aim of this study was to evaluate the thyroid hormones in patients with β TM in a children's hospital in New Delhi, India.

Materials and Methods: 68 patients (aged 1-12 years) with β -thalassemia major that undergo periodical blood transfusion at Chacha Nehru Bal Chikitsalya Hospital, New Delhi were included in the study. The diagnosis was based on clinical examination and haematological and haemoglobin electrophoresis profile. Serum levels of ferritin, iron, thyroid hormones FT3, FT4 and TSH levels along with bilirubin and transaminases were estimated in all children.

Results: Subclinical hypothyroidism was observed in 23 patients (34%), who were further divided into 2 groups: - compensated hypothyroidism which included 16 patients (24%) and decompensated hypothyroidism with 7 patients (10%). 45 patients (66%) were found to be euthyroid. No significant worsening of thyroid profile was observed after one year of study.

Conclusion: Hypothyroidism is a frequent complication of excess iron load in thalassemia major patients. It is not clinically observed in most thalassemia major patients and regular monitoring for the early detection and timely treatment of the disorder should be implemented in all thalassaemic children.

Keywords: β -thalassemia major, Iron overload, Ferritin, Thyroid hormones, Hypothyroidism.

INTRODUCTION

β -thalassaemia major (β -TM), is a type of chronic, inherited, microcytic anemia characterized by impaired biosynthesis of the β -globin leading to accumulation of unpaired α -globin chain¹. In India more than 10,000 children are born with β -thalassemia major (BTM) every year². Transfusion related iron overload is the primary therapeutic complication in thalassemia major. A wide range of literature has documented multiple organ dysfunction amongst chronically transfused thalassaemic patients amongst which the heart, liver, and endocrine systems are the most commonly affected³. Other factors like hypoxia due to persistent anemia, perfusion defect and poor nutrition, chelating agents, liver disease and genetic susceptibility may also contribute to the derangement⁴⁻⁶. Hypothalamic–pituitary –thyroid axis, para-thyroid, adrenal,

pancreas, gonads, all may show hypo-activity. Frequency of hypothyroidism varies from 6 to 30% in thalassaemic patients amongst different countries depending upon on their chelation regimens⁷. Lower prevalence is found in patients with decreased iron load as measured by serum ferritin levels⁸. The prognosis depends on the amount and the duration of iron overload. Although numerous studies have been performed on endocrine complications in thalassemia, the number of published studies in Indian paediatric patients is significantly small. Therefore the aim of the present study was to evaluate the thyroid hormones in patients with β TM in a children's hospital in New Delhi, India.

MATERIALS AND METHODS

The present case control study was conducted in Chacha Nehru Bal Chikitsalya Hospital, New Delhi from 1st October

2012 till 31st September 2013. The study included 68 patients 39 male and 29 female with β -thalassemia major. All of them were on a blood transfusion program in thalassemia center at CNBC Hospital. The diagnosis of BTM was made by clinical examination, peripheral blood smear and hemoglobin electrophoresis. Any subject with history of chronic inflammatory disease or haematological disorder was excluded from the study. Patients received regular blood transfusions every 2-3 weeks to maintain haemoglobin level at 9 to 10.5. All the patients were on oral iron chelation therapy with deferasirox in a dose of 10-30 mg/kg/day. Individual dosing was determined by patients clinical and laboratory assessments, such as iron overload indices and other comorbidities. Records were analyzed with respect to age at diagnosis, age at first transfusion, mean transfusion requirement, duration of transfusion and total blood received. All patients were vaccinated with Hepatitis B vaccine. The study was approved by the ethics committee and informed consent was taken from all the subjects or parents prior to participation in the study. 6 mL of venous blood was collected using aseptic precautions prior to blood transfusion. 2mL of blood was collected in an EDTA tube for estimation of Hb and analysed on MS-9 hematology device. The remaining blood was allowed to clot and centrifuged at 5000 rpm for five minutes. The separated serum was then used for estimation of ferritin and thyroid hormones FT3, FT4 and TSH levels which were assessed by chemiluminescence method using Access-2 Beckman Coulter analyser. Serum bilirubin, transaminases and iron were estimated on Olympus AU-400 analyser. The normal range for the various hormones were as follows: - FT3: 2.39-6.79 pg/mL, FT4: 0.58-1.64 ng/dL and TSH: 0.34-5.60 μ IU/mL. On the basis of their thyroid profile the thalassemic patients were further divided into euthyroid, compensated hypothyroid and decompensated hypothyroid. Thyroid function tests were repeated in the thalassemia major patients after one year.

STATISTICAL ANALYSIS

Data was expressed as mean \pm standard deviation values. The data between the euthyroid and hypothyroid cases was analyzed by using student's unpaired t test. Pearson's correlation test was used to define the correlation between thyroid hormones and ferritin. A p-value of less than 0.05 was accepted as statistically significant. All statistics were performed by using SPSS for windows 12.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The present study included 68 patients with β -thalassemia major with a mean age of 8.8 ± 2.7 years (range 1-12 years) amongst which 39 were male and 29 female. Table No.1 shows the demographic, haematological and biochemical parameters of the thalassemic patients under study. There was no significant difference between the euthyroid and hypothyroid thalassemics regarding their age of 1st transfusion and no. transfusion packs in one year. While comparing biochemical profile of the euthyroid thalassemics (n = 45) and hypothyroid thalassemics (n = 23) we observed serum ferritin level of the hypothyroid patients (3440.06 ± 532.80 ng/dL)

comparable to that of the euthyroid cases (3284.61 ± 636.80). Serum iron, bilirubin, transaminases and Hb levels were also comparable amongst the two groups. As shown in Table No.2 thyroid dysfunction was observed in 23 patients (34%), who were further divided into 2 groups: - Group 2 and Group 3 i.e compensated hypothyroidism which included 16 patients (24%) and decompensated hypothyroidism with 7 patients (10%). 45 patients (66%) were found to be euthyroid (Group 1). None of the patients in Group 2 and Group 3 showed any clinical signs and symptoms of hypothyroidism. As shown in Table No.3 thyroid function tests were repeated in the patients after one year, no significant changes were found in their proportions.

DISCUSSION

Thyroid hormones are important for the proper development, differentiation and metabolism of cells. Thyroid dysfunction has been reported in a number of studies on thalassemia patients. A wide range of pathogenic mechanisms may be involved. Tissue chronic hypoxia and iron overload have a direct toxic effect on the thyroid gland⁹. High concentrations of labile plasma iron and labile cell iron may lead to the formation of free radicals and the production of reactive oxygen species resulting in cell and organ damage¹⁰. In severe iron overloaded thalassemic patients the anterior pituitary may also be damaged and regulatory hormonal secretion (LH, FSH, and TRH) may be disrupted¹¹. Organ siderosis (liver, cardiac and skeletal muscle, kidney) may affect specific receptors, which regulate thyroid hormone action and convert T4 to the bioactive T3. In our study subclinical hypothyroidism (compensated or decompensated) was observed in 34% of the thalassemic patients. Overall 1/3rd of the patients in this study were hypothyroid. Serum FT3 levels were normal in all the patients, similar findings are observed in thyroid hormones in different disease aetiologies¹². Although we found no evidence of clinical hypothyroidism in our study it has been reported as 6.9% by Agrawal¹³ and his co-workers, 4% by Zervas et al¹⁴, 18.3% by Magro et al¹⁵, and none by Phenekos et al¹⁶ as the index study. No significant difference was found in the iron overload as measured by serum ferritin in the thalassemic euthyroid and hypothyroid patients. Similar findings were observed by Al-Hader et al¹⁷, Cavallo and his co-workers¹¹ and Filosa et al¹⁸. We also observed no correlation between serum ferritin and thyroid status in the present study. Similar observations have been found for diabetes mellitus as well. This suggests that other factors apart from iron over-load may play a role in the endocrine damage. The present study showed no relationship between age, liver dysfunction, transfusion regimen and endocrine damage. Our findings were in accordance to a study by Jain et al¹⁸, who observed that thyroid dysfunction was not related to age, sex, hemoglobin levels and country of origin. Transfused iron load (units/kg/year) were higher in patients with hypothyroidism, however, the difference was not found to be statistically significant¹¹. We found no significant worsening of thyroid profile after one year of study. However in a study by Filosa et al¹⁹ the proportion of hypothyroidism increased from 8.4% to 13.9 % over a period of 12 years in thalassemic patients. Since

the follow up period of one year was too short to pick up worsening of thyroid profile a longer follow up is recommended in further studies.

CONCLUSION

The following study showed hypothyroidism as a frequent complication of excess iron load in thalassemia major patients. Hypothyroidism is not clinically observed in most thalassemia major patients and regular monitoring for the early detection and timely treatment of the disorder should be implemented in children.

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Table 1: Demographic, Haematological and Biochemical Parameters in Thalassaemic Patients

PARAMETERS	Hypothyroid patients (N=23)	Euthyroid patients (N=45)	p-value
Age at 1 st transfusion in years	1.99 ± 0.41	1.94 ± 0.27	P > 0.05
Transfusion packs (in 1 year)	20.85 ± 4.92	19.82 ± 5.01	P > 0.05
Iron overload (mg)	2349.87 ± 199.81	2338.65 ± 204.21	P > 0.05
Hemoglobin (gm/dL)	8.35 ± 0.51	8.46 ± 0.44	P > 0.05
Serum Ferritin	3440.06 ± 532.80	3284.61 ± 636.80	P > 0.05
SGOT	73.22 ± 86.48	72.15 ± 79.68	P > 0.05
SGPT	61.54 ± 49.65	63.81 ± 52.13	P > 0.05
Serum Bilirubin	1.37 ± 0.57	1.39 ± 0.71	P > 0.05

Table 2: Thyroid Function Tests in 3 Groups

GROUPS	FERRITIN (ng/mL)	FT3 (pg/mL)	FT4 (ng/dL)	TSH (μIU/mL)
Group1:-Euthyroid (N = 45)	2250.48 ± 557.3	3.46±1.39	0.92 ±0.31	3.75± 1.41
Group2:-Compensated Hypothyroid (N = 16)	3360.81 ± 504.7	3.98±1.53	1.08± 0.33	8.81 ±2.68
Group3:-Decompensated Hypothyroid (N = 7)	3440.65 ± 636.8	5.04± 3.78	0.43± 0.41	7.14 ±9.23

Table 3:- Thyroid Function Tests at Start and after 1 year in Thalassaemia patients

THYROID FUNCTION TESTS	AT START	AFTER 1 YEAR	p-value
FT3 (pg/mL)	3.58 ± 1.43	3.62 ± 1.11	P > 0.05
FT4 (ng/dL)	0.91 ± 0.35	0.88 ± 0.54	P > 0.05
TSH (μIU/mL)	5.48 ± 3.12	5.11 ± 3.28	P > 0.05

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