ASSESSMENT OF STATUS OF THYROID FUNCTIONS IN PATIENTS OF β THALASSEMIA MAJOR, REPORTING TO OPD OF MILITARY HOSPITAL, RAWALPINDI

Kanwal Jehanzeb, Farooq Ahmad*, Munir Akmal Lodhi, Salman Ali*****

Combined Military Hospital Lahore / National University of Medical Sciences (NUMS) Pakistan, *Combined Military Hospital Gilgit. National University of Medical Sciences (NUMS) Pakistan **Military Hospital / National University of Medical Sciences (NUMS) Rawalpindi Pakistan, ***Army Medical College / National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the status of thyroid functions in patients of β Thalassemia Major, reporting to OPD of Military Hospital, Rawalpindi.

Study Design: Descriptive cross sectional study.

Place and Duration of Study: Paediatric Outpatients Department of Military Hospital, Rawalpindi from 1st Jan to 30th Jun 2012.

Material and Methods: After taking informed consent from the parents of all the children fulfilling the inclusion criteria, detailed history was taken and blood samples were drawn by strict aseptic means. Samples taken from these patients included complete blood and thyroid profile (serum thyroxine T4, triiodothyronine T3 and thyroid stimulating hormone TSH). These blood samples were labeled and sent to Armed Forces Institute of Pathology (AFIP), Rawalpindi for analysis by enzyme-linked immunosorbent assay (ELISA). Primary hypothyroidism was defined by TSH levels >4IU/ml. Statistical analysis was done at the end of study using SPSS version 10. Significance for association was calculated using student t-test.

Results: Sixty patients fulfilled the inclusion criteria out of these sixty four patients lost the follow up while 56 patients completed the study. Out of 56 patients, 21 (37.5%) had biochemical evidence of hypothyroidism. Mean Ferritin level was 3924 ± 1247ng/ml in hypothyroid and 3136 ± 1387ng/ml in euthyroid patients indicating a significant difference in mean serum ferritin levels between hypothyroid patients and others.

Conclusion: The study demonstrates hypothyroidism in a significant number of hyper transfused β- thalassemic patients, emphasizing the importance of monitoring thyroid functions in thalassemic patients, particularly in those receiving suboptimal chelation.

Keywords: Beta thalassemia major, Chelation therapy silicone, Hypothyroidism, Iron overload.

INTRODUCTION

Thalassemia is an inherited autosomal recessive blood disorder. There are estimated 60-80 million people in the world who carry beta thalassemia trait alone[1]. This disease is particularly prevalent among people of Cyprus (14%), Sardinia (10.3%) and South East Asia[2]. In Southeast Asia, gene frequencies of alpha thalassemia reach 30-40% and beta thalassemia gene frequencies varies between 1-9%[3]. The incidence in Pakistan was 25.7%[4].

Treatment of patients with β-thalassemia major includes long term blood transfusions, iron chelation, splenectomy and bone marrow transplantation. Complications of thalassemia include transfusion related infections as hepatitis C, HIV, complications due to iron overload which include cardiac complications like hypertrophic cardiomyopathy, arrhythmias, and cardiac failure and endocrinopathies like hypothyroidism, hypoparathyroidism, gonadal failure, pubertal delay, short stature and diabetes mellitus[5,6].

Thyroid dysfunction is reported in 26% patients with β-thalassemia major, but its severity and frequency varies in different cohorts according to chelation regimens[5-7]. Thyroid hormones are critical determinants of brain and somatic development in infants and of metabolic

Correspondence: Dr Farooq Ahmad, Child Specialist CMH Gilgit Pakistan (*Email: tahafarooq2010@live.com)*
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activity in children and adults, affecting the function of virtually every organ. T4, T3 secretion by thyroid gland is tightly regulated by hypothalamo-pituitary-thyroid axis[8,9]. Thus iron overload related hypothyroidism may be either central or primary depending upon the deposition of iron on pituitary, hypothalamus or thyroid gland itself. Since thyroid hormone affects various systems of body like cardiovascular system, nervous system, reproductive digestive system, and adrenals and also causes anemia; this study was planned to assess the status of thyroid functions and to treat (with thyroid hormone and/or chelation) and prevent hypothyroidism by regular chelation therapy in patients of β-Thalassemia major.

Table-I: Description of thyroid function status, age and number of transfusions in thalassemia major patients (n=56).

	Minimum	Maximum	Mean	Std. Deviation
Age in Months	3	30	8.98	5.70
Number of Transfusions/year	12	24	16.68	4.48
Serum Ferritin	160.00	15000.00	4152.3214	3402.0304
T4	.62	19.70	11.5064	3.0182
T3	.70	12.00	2.3636	1.8445
TSH	.25	75.00	7.0598	13.2941

Table-II: *p*-value for gender and thyroid status.

	Hypothyroid	Euthyroid	***p*=0.314**
Male	12	15	Odd ratio=1.86
Female	6	14	95%CI=0.47-7.59

Table-III: Association of ferritin levels (ng/ml) in Hypothyroid and Euthyroid through student t-test.

Parameter	Hypothyroid	Euthyroid	*p*-value
Serum ferritin	Mean-3924 SD ± 1247	Mean-3136 SD ± 1387	0.0373

Clinical hypothyroidism manifests as lethargy, decreased appetite, cold intolerance, weight gain etc.

The aim of this study was to determine the frequency of hypothyroidism in children suffering from thalassaemia major.

MATERIAL AND METHODS

This descriptive cross sectional study was conducted at paediatric outpatients department of Military Hospital Rawalpindi and was completed in six months. It was started after the approval from ethical committee of the hospital. Informed consent was obtained from the parents of the children. Sample size was calculated by WHO sample size calculator, using 95% confidence level, prevalence 35% and absolute precision required 10% and population proportion of 43.56%. Sample size (60) was completed in six months. Consecutive (non-probability) sampling technique was used for data collection.

Inclusion criteria: diagnosed patients of thalassaemia major, age group from 4-18 years, children from both gender, resident of Rawalpindi with past history of more than 5 blood transfusions. Exclusion criteria: all the patients with hypothyroidism due to causes other than iron overload confirmed from history (like congenital hypothyroidism or family history of hypothyroidism). The patients were booked at Military Hospital Rawalpindi and they were later followed up for compliance with the treatment given and the results were noted in their respective folders. Hypothyroidism is defined as TSH level more than 4 μIU/ml, T4 less than 4.5 μg/dl

and T3 less than 82 ng/dl. The thyroid function tests were classified as sub-clinical (increased TSH, normal T3 and T4), clinical (increased TSH, low levels of T3 and T4) and euthyroid (normal TSH, normal free T4).

Diagnosis was confirmed on usual hematological criteria which included peripheral blood evaluation and Hb electrophoresis. Detailed history was taken keeping in account the age of presentation, number of blood transfusions and method of chelation. Every child was assigned a serial number. Blood samples were drawn under strict aseptic means. Samples were labeled, and sent to AFIP Rawalpindi for analysis. Serum Ferritin levels were obtained from the patients' records and the most recent values were recorded for analyses.

Data were analyzed by using Statistical Package for Social Sciences (SPSS) software version 10.0. Mean and standard deviation (SD) were calculated for quantitative variables (age, number of blood transfusions in a year, thyroid profile and serum Ferritin) using t-test. Frequencies and percentages were calculated for qualitative variables like gender using chi-square.

RESULTS

A total of 300 patients with confirmed diagnosis of beta thalassemia major reported to Pediatric OPD during the study period. Of these 60 patients fulfilling the inclusion criteria were enrolled in the study. Four patients were later lost to follow up while 56 patients completed the study. Results of the investigations were entered in the standard proforma. Parents of the most of the enrolled children were army personnel, representing all provinces of the country. Fathers of the most of the enrolled children had education at least up to matriculation as being the army personel. At the end of the study data obtained were analyzed using Statistical Package for Social Sciences (SPSS) software version 10.0. Results showed twenty four (42.9 %) of them were female and 32 (57.1%) were male. Mean age of patients was 7.16 ± 4.06 years. The patients were diagnosed (as beta thalassemic) between three to thirty months of age with mean age of diagnosis being 8.98 ± 5.70 months. Number of transfusions per year ranged from 12-24. Mean hemoglobin (Hb) levels before and after blood transfusions were reported as 8.7 ± 0.6 and 12.8 ± 1.2 table-I. All patients were on chelation therapy with 31 (55.4%) being on oral chelation while 25 (44.6%) were on subcutaneous chelation. Twenty one (37.5%) patients had biochemical evidence of hypothyroidism fig-1. Of these 12 (57.1% of hypothyroid) were male and 9 (42.9% of hypothyroid) were female. No significant association of gender with thyroid status was found table-II.

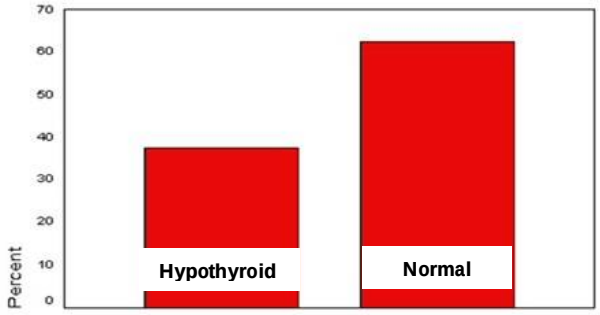

Figure-1: Thyroid function in thalassemia major patients.

We also noticed very high serum ferritin levels in some of our enrolled patients. Significance for association was calculated using student t-test. The student t-test revealed *p* value =0.0373, stating that the difference in mean ferritin levels of both groups was significant (table-III).

DISCUSSION

The frequency of hypothyroidism in thalassemia patients ranges from 6 to 30% among different countries depending on chelation regimens. Lower prevalence was found in patients who had evidence of lower iron load as measured by ferritin levels[10-12]. Thyroid dysfunction has been variably reported in thalassemia patients[13-15]. Subclinical hypothyroidism was observed in 37.5% of thalassemia patients in our study. Although we found no case of clinical hypothyroidism in our study group, it was reported in 6.9% by Agrawal

et al, 4% by Zerves et al, and 18.3% by Morgo et al [13,14,16].

We found no correlation between thyroid dysfunction and age, amount of blood transfusion. Similar results have been documented in various studies. Jain et al, observed that thyroid dysfunction was not related to age, sex, hemoglobin levels and country of origin, but transfused iron load (units/kg/year) was higher in patients with hypothyroid function, however, the difference was not statistically significant[17]. In another study, the mean serum ferritin levels were 3390 ± 135.6 ng/ml. Only two patients (2.67%) had serum ferritin levels of less than 1000 ng/ml. Sixteen patients (21.34%) had serum ferritin levels between 1000–2500 ng/ml, while 57 patients (76%) had values more than 2500 ng/ml[18]. The ferritin level was significantly raised in hypothyroid patients than euthyroid patients. This iron overload causes damage at cellular level and in similar manner it affects the production of thyroid hormone in these patients. Hence, the need of intensive chelation is necessary to avoid such complication. Chelation regimes are oral as well as subcutaneous. Hypothyroidism may be partly related to the accumulation of iron in thyroid gland due to blood transfusion by iron overload leading gland dysfunction[19].

At the thalassemia center of Military Hospital, blood transfusion is carried out of patients when haemoglobin is ≤10 g/dl, while in some of the other studies, the pre-transfusion Hb levels were maintained at ≤8 g/dl. Despite the high prevalence of hypothyroidism in our study, all subjects were clinically euthyroid, similar to most of previous studies[14,15,18]. One of the limitations of this study was that the measurement of variables was only conducted once. In addition, the data on adherence to regular chelation therapy relied entirely on parents/guardians reports making it prone to recall bias. The data on the cumulative volume of blood received by the subjects since they were first diagnosed was taken entirely from data in the subjects' medical records in Military Hospital. However, because Military Hospital is a teaching hospital, where the quality of its medical records is presumed to be reliable. The fairly high prevalence of hypothyroidism in this study suggests the importance of regular thyroid function monitoring for pediatric beta thalassemia major patients, in order to detect and implement early treatment.

CONCLUSION

This study demonstrated hypothyroidism in a significant number of hyper transfused β-thalassemic patients, who received suboptimal iron chelating therapy. These finding emphasizes the importance of monitoring of thyroid function in all hypertransfused thalassemic patients, particularly who received suboptimal chelation therapy.

Patients who have elevated TSH levels should be followed-up yearly. As pharmacological treatment for hypothyroidism is readily available, it is important to monitor thyroid function in these patients and institute prompt therapy when indicated. Iron overload induced hypothyroidism may respond to adequate chelation therapy promoting prevention or/and reversal of the disease and other associated co morbidities. In addition, therapy with L-thyroxin should be considered in hypothyroidism in thalassemia major patients.

RECOMMENDATON

Early systematic laboratory evaluation and treatment of thyroid dysfunction is recommended in all thalassemic patients annually. In addition to iron chelation, therapy with L-thyroxin should be considered in hypothyroid beta thalassemia major patients with moderate to severe iron overload.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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