FREQUENCY OF HYPOTHYROIDISM IN MULTI-TRANSFUSED IRON OVERLOADED ß-THALASSEMIA SYNDROME PATIENTS

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ABSTRACT

Background: Beta thalassemia syndromes are heterogeneous inherited disorders. They represent the commonest inherited hemoglobinopathies and constitute a com-mon public health problem. Patients suffering from these disorders ultimately devel-op complications including endocrinopathies secondary to transfusional iron over-load. Thyroid dysfunction is well documented in this context; however there is great disparity in its prevalence across the world. This study was designed to determine the frequency of thyroid dysfunction in multi-transfused (> 12 regular transfusions) beta thalassemia syndrome patients in District Peshawar Pakistan.

Methodology: In this cross-sectional descriptive study, patients treated at Fatimid Foundation Peshawar were enrolled. One hundred and fifteen multi-transfused beta thalassemia syndrome patients >10 years of age were included. Data and blood samples were collected after taking written informed consent from patients/guardians. Venous blood (3ml) was collected in vacuette® (Griener, GmbH). After centrifugation, sera were separated and analyzed for T_4, T_3, TSH and ferritin levels by Chemiluminescence Immune Assay (CLIA) technique using Acculite Monobind Diagnostics on Lumax analyzer in IBMS.

Results: Primary subclinical hypothyroidism was detected in 25 (21.7%) pa-tients. All patients were iron overloaded as indicated by very high serum ferri-tin levels (ranging from 1500-27042ng/ml).

Conclusion: Hypothyroidism occurs mainly in subclinical state and is a fre-quent complication in iron overloaded beta thalassemia syndrome patients with risk of progression.

Key Words: Beta thalassemia syndrome, iron overload, thyroid dysfunction.

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INTRODUCTION

Beta thalassemia syndromes refer to a group of in-herited disorders with diverse clinical manifestations ranging from mild asymptomatic microcytic anaemia to severe anaemia requiring regular red cell transfusions[1]. These disorders are often diagnosed inadequately and include beta thalassemia trait, beta thalassemia inter-media, beta thalassemia major and beta thalassemia compound heterozygotes. They are caused by mutations or deletions in beta globin genes leading to reduced or absent beta globin chain while synthesis of alpha chain remains unaffected. The excess alpha chains precipi-tate in erythroid precursors and lead to their premature destruction and abnormal maturation in the bone mar-row[2]. The result is a dyserythropoietic state and hemo-lysis in homozygotes and compound heterozygotes[3].

Beta thalassemia syndromes are a common public health problem in Indian Subcontinent, Middle East, Southeast Asia and Africa. Globally, about 330,000 in-fants with inherited hemoglobinopathies are born annu-ally. These disorders account for approximately 3.4% of all deaths in under 5 years age group[4]. It is estimated that nearly 1.5% of global population are beta thalas-

semia carriers and the annual frequency of symptomatic individuals is expected to be 1 in 100,000 all over the world[5]. In Pakistan about 70,000 people are estimated to be suffering from thalassemias and every year 6000 newly diagnosed cases present for management[6].

Due to inadequate diagnosis patients are arbitrari-ly advised hyper transfusion regimens. It is estimated that 1 unit of whole blood contains about 200mg-250mg of iron[7] and packed red cell requirements in non-sple-nectomized patients are estimated to be about 160ml/ kg annually[8]. Chelation is conventionally started when serum ferritin reaches 1000ng/ml or when patient has received 10-20 transfusions[9,10]. Regular transfusions in the face of inadequate chelation especially in develop-ing world leads to iron overload. There is consequential growth retardation, osteopenia, metabolic and endo-crine disorders along with skeletal changes, cardiac and other system disorders.

Thyroid gland dysfunction is well documented in con-text of thalassemia major. The dysfunction occurs main-ly in the form of primary hypothyroidism which is char-acterized by an elevated TSH in the face of normal or reduced T_3 and T_4. Several studies conducted worldwide report the prevalence of hypothyroidism in the order of 6% to 50% of multi-transfused beta thalassemia major patients[11,12]. It develops due to transfusional iron over-load with subsequent deposition of iron in thyroid gland particularly from the second decade of life[13,14].

Studies conducted in different countries have shown that primary subclinical hypothyroidism occurs more frequently than overt hypothyroidism, though there is enormous disparity in its prevalence across the world[15]. Signs and symptoms attributed to thyroid dysfunction are highly nonspecific but virtually affect every organ system. So lab evaluation of these patients is crucial to identify the patients who have developed or who are at risk of developing thyroid dysfunction.

METHODOLOGY

This cross-sectional descriptive study was carried out at the Institute of Basic Medical Sciences (IBMS), Khyber Medical University (KMU), Peshawar, from March 2014 to March 2015. One hundred and fifteen multi-transfused (more than 12 regular blood transfusions) beta thal-assemia syndrome patients more than 10 years of age were included in the study. Patients already receiving thyroid hormone replacement therapy, patients with other comorbid conditions, goiters and family history of thyroid disorders were excluded. Patients treated at Fatimid Foundation were enrolled after taking permis-sion from concerned authorized personnel in Fatimid Foundation. The study was commenced after approv-al from AS&RB (Advanced Studies and Research Board) and Ethical Board of KMU. Written informed consent was taken prior to detailed history, clinical examination and blood sampling. A volume of 3ml of venous blood was collected directly in vacuettes® from each patient. Serum was extracted from each sample after centrifu-gation and analyzed for TSH, fT_4, T_3 and ferritin levels by Chemiluminescence Immune Assay (CLIA) technique using Acculite Monobind Diagnostic kits on Lumax® ana-lyzer Monobind Inc. USA (a Chemiluminescence micro-plate reader).

Biochemical tests were performed in the laboratory of Institute of Basic Medical Sciences, Hayatabad Pesha-war after taking permission from Head of Deptt, Hae-matology. The tests were run in a single batch along with positive and negative controls and calibrators for each test to assess quality assurance. All data were fed into computer program Statistical Package for Social Sciences (SPSS) version 16.0. Frequencies and percent-ages were calculated for categorical variables. Mean ± SD were calculated for numerical variables.

RESULTS

Out of 115 patients, 67 (58.3%) were male and 48 (41.7%) were female. Majority of the patients (86.1%) were Pathans, the rest belonging to other ethnic groups of Pakistan. The mean age of the study population was 18.47 years (ranging from 13-32 years). Majority of the patients (53.0%) were in 16-20 years age group. Hepa-titis screening of patients revealed 32 as HCV positive. Out of total, 29 (25.2%) patients were splenectomized.

Eighty one (70.4%) patients were receiving iron che-lation therapy, although only 03 patients were compli-ant to it. The main reason was unaffordability, cumber-some regimen of subcutaneous desferrioxamine being the second main cause.

All patients were iron overloaded as indicated by very high serum ferritin levels (ranging from 1500-27042 ng/ml). Percentage of patients with respect to severity of iron overload is illustrated in Fig 1.

Primary subclinical hypothyroidism was detected in 25 (21.7%) of the subjects as indicated by high serum TSH and normal free T_4 and T_3 levels.

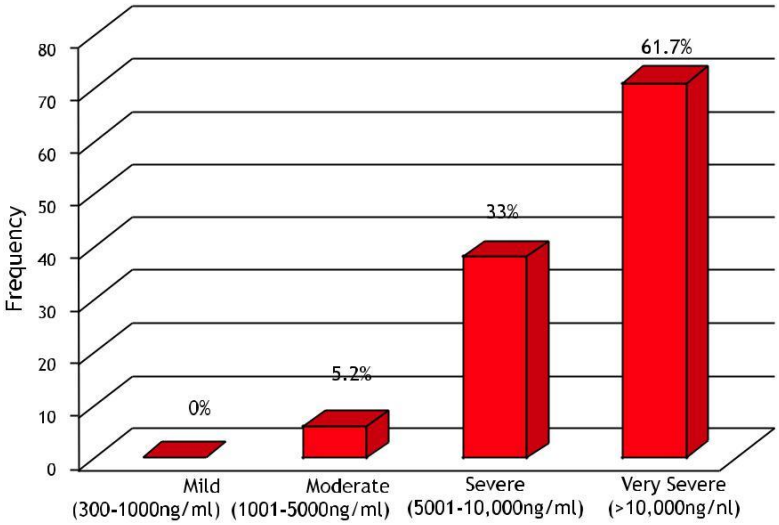

Figure 1 Bar chart showing frequency and percentage of patients with mild, moderate, severe and very severe iron overload based upon serum ferritin levels

Table 1 Salient demographic/clinical characteristics of study population

Variables		Frequency (%)
Gender	Male	67 (58.3)
	Female	48 (41.7)
Age Groups (years)	10-15	28 (24.3)
	16-20	61 (53.0)
	21-25	20 (17.4)
	> 25	06 (5.2)
Chelation	Yes	81 (70.4)
	No	34 (29.6)
Status of Chelation	Compliant	03 (2.6)
	Non-compliant	78 (67.8)
Splenectomy	Yes	29 (25.2)
	No	86 (74.8)
HBV/HCV Status	Unknown	76 (66.1)
	Both positive	01 (0.9)
	Both negative	04 (3.5)

Table 2 Descriptive statistics of study patients (N=115)

Variables	Range	Minimum	Maximum	Mean ± SD
Age (years)	19	13	32	18.47 ± 3.626
Weight (kg)	54	16	70	35.58 ± 9.258
Height (cms)	57	113	170	143.67 ± 11.244
S. Ferritin (ng/ml)	25542	1500	27042	. 11976 ± 5042.354

N, sample size; SD; Standard Deviation.

Table 3 Thyroid function tests in euthyroid and hypothyroid groups

Thyroid Function Tests	Euthyroid (n= 90) Mean ± SD	Hypothyroid (n=25) Mean ± SD
TSH (μIU/ml)	2.1693 ± 1.101	11.0524 ± 12.07
fT4 (ng/dl)	1.45 ± 0.3370	1.272 ± 0.2909
T3 (ng/ml)	1.52 ± 0.1727	1.396 ± 0.2835

n; frequency, SD; standard deviation, S. TSH; serum thyroid stimulating hormone, S. fT4; serum free thyroxine, S. T3; serum total tri-iodothyronine

Table 4 Thyroid function status in categories of moderate, severe and very severe iron overload

			Severity of iron overload			Total
			Moderate	Severe	Very Severe	
Thyroid function stat status	Euthyroid	Frequency	05	30	55	90
		% of Total	4.3%	26.1%	47.8%	78.3%
	Hypothyroid	Frequency	01	08	16	25
		% of Total	0.9%	7.0%	13.9%	21.7%
Total		Frequency	06	38	71	115
		% of Total	5.2%	33.0%	61.7%	100.0%

Patients with very severe iron overload as indicated by serum ferritin levels more than 10,000ng/ml constituted 61.7% of the study population. None of the patients had serum ferritin levels less than 1000ng/ml (mild iron overload). Subclinical hypothyroidism was found to be 0.9%, 7.0% and 13.9% in patients with moderate, severe and very severe iron overload as shown in table 4.

DISCUSSION

There is enormous disparity in prevalence of hypothyroidism with some studies reporting it in a low range of 0-12%[16,17] whilst others showing a high prevalence of 16-35%[18]. These discrepancies in its prevalence can be attributed to the differences in ages of study popula-tion, treatment protocols, compliance to treatment and chelation therapy regimens being practiced in different countries[19].

In present study, multi-transfused beta thalassemia syndrome patients were evaluated for thyroid function. Isolated elevation of TSH was detected in 25 (21.7%) patients which was consistent with the diagnosis of primary subclinical hypothyroidism, whilst overt state of disorder was not observed in the present study. This high prevalence was most likely attributed to subopti-mal iron chelation therapy as evidenced by very high levels of serum ferritin.

Our study results are comparable to a Pakistani study conducted by Malik et al[20] where, 25.7% of beta thalas-semia major patients had primary hypothyroidism and of those, 21.25% had subclinical hypothyroidism Like-wise, in another study in India, 20% of beta thalassemia major patients were diagnosed to have subclinical hy-pothyroidism[21].

In contrast to present study, a low prevalence of hypothyroidism (7.7%) was observed by Shamshirsaz et al, who assessed thyroid function in 220 beta thalassemia patients in Tehran[22]. Similar result was reported by Hashemizadeh et al[13]. Prevalence of hypothyroidism observed in various studies is shown in table 5 below.

Our study was confined to a single center and includ-ed patients of age above 10 years. In most of patients the exact diagnoses was uncertain. They were diag-nosed only on the basis of raised HbF (fetal hemoglo-bin) fifteen to twenty years ago and were labelled and managed as beta thalassemia major. Although majority of the patients clinically appeared to be intermediate category of beta thalassemia syndrome.

Handling of iron is different in patients of beta thalassemia major and intermedia. Thus the etiology of iron overload with subsequent deposition of iron in the body is also different.

It is therefore suggested to perform a multi-center

study with larger sample size. Inclusion of patients less than 10 years of age is recommended to assess the trend of endocrinopathy in different age groups and to determine whether hypothyroidism also occurs in the younger age groups. PCR based genetic diagnosis of these pa-tients is crucial. It will not only improve their manage-ment but will also help to understand the mechanisms of iron overload and prevalence of endocrinopathy in thalassemia major and intermedia groups.

CONCLUSION

In our study, thyroid dysfunction was detected in the form of primary subclinical hypothyroidism. We observed that the endocrinopathy was equally prevalent in patients of age 10-18 years and above.

Thus it is concluded that thyroid dysfunction develops frequently in multi-transfused beta thalassemia syn-drome patients secondary to iron deposition. Although it occurs frequently in subclinical state, nevertheless there is risk of progression to overt state. This signi-fies the need for appropriate treatment, optimal chela-tion and regular surveillance of these patients, thereby improving the quality of life (QOL) of multi-transfused beta thalassemia syndrome patients.

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