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Thyroid Profile in Multitransfused B-Thalassemia Major Patients.

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Abstract:
Background: aim of this study was t*o determine the proportion and type of hypothyroidism in patients with β-thalassemia major.*
Methods: *This study was conducted in department of Pediatrics, Sir Padampat Mother & Child Health Institute, SMS medical college, Jaipur. It was a Hospital based cross sectional study for a period of 12 months from April 2015 to march 2016. Cases with confirmed diagnosis of β-thalassemia major that were on regular blood transfusions and 3 to 18 years of age (both sexes) and free from any other chronic diseases were included. Patients were subjected to a detailed history and physical examination. Blood samples for hemogram, serum ferritin level, S. Free T_4, T_3 and TSH level, Anti-TPO Antibody levels were taken.*
Results: *The study included 90 children of both sexes with thalassemia major within age-group 3-18 years. Out of these 69 (76.67%) were male and 21 (23.33%) female. Male to female ratio was 3.3:1.The mean age for the male patients was 9.07±4.02 years and for female patients, it was 9.09±3.45 years. Thyroid function tests were normal in 76 (84.44%) patients and rest 14 (15.56%) had abnormal thyroid function tests. Out of these 14 patients, 9 (10%) patients had subclinical hypothyroidism while 5 (5.56%) patients had central hyperthyroidism. No case with overt hypothyroidism and primary hypothyroidism was present. Subclinical hypothyroidism was most prevalent in the age group of 6-8 years (44.45%) while central hypothyroidism was most prevalent in the age group of >12 years (80%). Age of diagnosis of thalassemia for patients with normal thyroid function was 16.01±11.37 months; for subclinical hypothyroidism was 13.44±9.56 months; and for central hypothyroidism was 15.80±7.65 months. No significant correlation was found between the age of the diagnosis of the thalassemia and the thyroid dysfunctions of the subjects. (p>0.05). The mean value of serum ferritin in euthyroid patients was 2029.80±1163.38 ng/mL; for subclinical hypothyroidism was 2477.33±1062.95 ng/mL; for central hypothyroidism was 2914.00±930.54 ng/mL. No significant correlation was found between thyroid dysfunctions and the serum ferritin levels of the subjects (p>0.05) . No significant correlation was found in thyroid dysfunctions in the study subjects and Anti-TPO antibody status of the subjects. The mean number of blood transfusions in euthyroid patient was 113.74 ± 73.13; for subclinical hypothyroid was 123.78±81.11; for central hypothyroid was 208.60±41.90. Statistically significant correlation was found between thyroid dysfunctions and number of blood transfusions in subclinical and central hypothyroidism (p<0.05).*

Conclusions: *Subclinical hypothyroidism is common endocrinal complication in thalassemia patients. We should be more vigilant in screening patients for subclinical hypothyroidism so that treatment could be started at an earlier stage. Hypothyroidism was not correlated with serum ferritin level of the patients but it was related with the number of blood transfusions. So patients might have hypothyroidism despite of controlled serum ferritin level and proper chelation therapy.*

Key Words: *thalassemia, hypothyroidism, endocrinal abnormality, children, multitransfused.*

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I. Introduction

The thalassemia represents the most common monogenetic disorder worldwide [1]. 4.83% of the world's population carries globin variants, including 1.67% of the population who are heterozygous for α-thalassemia and β-thalassemia. Endocrine abnormalities are among the most common complications of β-thalassemia major [2]. Thyroid dysfunction is a frequently occurring endocrine complication in thalassemia major, but its prevalence and severity is variable and the natural history is poorly described [3]. Up to 5% of thalassemic patients develop overt clinical hypothyroidism that requires treatment [4]. A much greater percentage has sub-clinical compensated hypothyroidism with normal Free T4 and T3 but high TSH levels. It usually occurs in severely anemic and/or iron overload thalassemic but is uncommon in optimally treated patients [5, 6].

The anterior pituitary is particularly sensitive to iron overload and there is defective TSH secretion in response to low Free T4 in thalassemic patients due to iron mediated injury. The deposition of iron in the pituitary gland and its deleterious effects on pituitary size and functions has been reported in many studies which disrupts hormonal secretion resulting in central (or acquired) hypothyroidism [7,8,9]. Autoimmunity has no role in the pathogenesis of thalassemia related hypothyroidism [5]. There is no doubt that iron overload has important role to play in thyroid and other endocrinal dysfunction in thalassemic patients, non-significant difference in ferritin levels between hypothyroid and euthyroid group suggests that there are other mechanism by which thyroid dysfunction occurs in these children.the damage of endocrine glands caused by chronic hypoxia might play a more important role than iron-overload [10]. Abnormal thyroid function may be reversible by proper chelation therapy if get detected at early stage. Investigation of thyroid function should be performed annually beginning at the age of 9 years [1]. Hence, this study was planned out to study the thyroid hormone profile of thalassemic children attending our thalassemia ward to achieve the goal of early diagnosis and early intervention and better understanding of this common but preventable disorder.

II. Aims & Objectives

To determine prevalence of hypothyroidism in, patients with β-thalassemia major and to identify the type of hypothyroidism in patients with β-thalassemia major.

III. Materials And Methods

This study was conducted in department of pediatrics, Sir Padampat Mother & Child Health Institute, SMS Medical College, Jaipur. It was a hospital based cross sectional study for a period of 12 months from April 2015 to march 2016. Cases with confirmed diagnosis of β-thalassemia major that were on regular blood transfusions and 3 to 18 years of age (both sexes) and free from any other chronic diseases were included. Those suffering from thalassemia intermedia, alpha thalassemia and other hemoglobinopathies were excluded.

Patients were subjected to a detailed history and physical examination. Blood samples were sent immediately to central laboratory SMS hospital where Free T3, Free T4, TSH, Ferritin, anti-TPO antibody levels all were assessed in 'immunoassay laboratory' by *'advia centaur XP'* machine by chemiluminescence immunoassay method. Hemogram was obtained from five part hematology analyser *'sysmax'* by electrical impedance method in laboratory of SPMCHI Jaipur.

IV. Statistical Analysis

Statistical analysis was performed with the *SPSS, version 16*. Quantitative data was expressed in mean ± SD. Qualitative data was expressed using observation 'Z' test. Significance of difference in mean ± SD was expressed using 'unpaired T' test. Values of $p < 0.05$ were considered statistically significant.

V. Results

The study included 90 children of both sexes with thalassemia major within age-group 3-18 years. Out of these 69 (76.67%) were male and 21 (23.33%) female. Male to female ratio was 3.3:1.the mean age for the male patients was 9.07±4.02 years and for female patients, it was 9.09±3.45 years. Thyroid function tests were

normal in 76 (84.44%) patients and rest 14 (15.56%) had abnormal thyroid function tests. Out of these 14 patients, 9 (10%) patients had subclinical hypothyroidism while 5 (5.56%) patients had central hypothyroidism. We classified the patients on the basis of their thyroid hormone profile. According to the thyroid hormone function tests patients were classified in appropriate category. Our classification was based only on the laboratory values of thyroid function tests; we did not considered clinical manifestations of the hypothyroidism.

Table no.-1 prevalence of hypothyroidism in study subjects (n=90)

Thyroid dysfunctions	No.	%
Normal	76	84.44
Subclinical hypothyroidism	9	10.00
Central hypothyroidism	5	5.56
Total	90	100.00

Table no.-2 classification of study subjects on the basis of laboratory reports

Type of hypothyroidism	Laboratory criteria	No. Of cases
Subclinical hypothyroidism	Raised TSH, normal T4	9
Overt hypothyroidism	Raised TSH, low T4	0
Primary hypothyroidism	Raised TSH, low T4	0
Central hypothyroidism	Low or normal TSH, low T4	5

We did not find any case that has low T4 associated with raised TSH. So, primary hypothyroidism was not present in any study subject. Out of total 90 cases, thyroid function test were abnormal in 14 subjects; 9 cases had normal T4 levels with a raised TSH values so subclinical hypothyroidism was present in 9 (10%) cases. Out of 90 cases, central hypothyroidism was present in 5 (5.56%) cases; in which T4 level were low and TSH was normal or low.

Table no. -4 laboratory values of different parameters in the Hypothyroid patients (n=14)

S. No.	Free T4 (pmol/l)	TSH (mIU/l)	Type of hypothyroidism	S. Ferritin (ng/ml)	No. Of blood transfusions	Anti-TPO antibody level
1.	15.44	5.85	Subclinical	2800	63	Negative
2.	12.74	6.69	Subclinical	1470	25	Negative
3.	16.08	6.84	Subclinical	2300	110	Negative
4.	13.25	6.08	Subclinical	2878	210	Positive
5.	14.41	5.65	Subclinical	1022	60	Positive
6.	12.90	11.49	Subclinical	1120	100	Negative
7.	15.05	7.94	Subclinical	2630	158	Positive
8.	14.41	6.40	Subclinical	4000	88	Negative
9.	16.83	9.41	Subclinical	4076	300	Negative
10.	8.10	1.35	Central	2600	250	Negative
11.	9.52	1.79	Central	2890	168	Negative
12.	7.97	1.94	Central	1500	225	Negative
13.	9.52	1.80	Central	3200	250	Negative
14.	7.06	3.69	Central	4380	150	Negative

Table no.-11 mean + SD of age of onset of disease according Thyroid dysfunctions (n=90)

	Thyroid dysfunctions		
	Normal	Subclinical hypothyroidism	Central hypothyroidism
Mean + SD (months)	16.01 1±1.37	13.44 ±9.56	15.80 ±7.65

Normal v/s subclinical hyperthyroidism = p > .05 ns
Normal v/s central hyperthyroidism = p > .05 ns
Subclinical v/s central hyperthyroidism = p > .05 ns

Mean age of diagnosis of thalassemia for patients with normal thyroid function was 16.01±11.37 months; for subclinical hypothyroidism was 13.44±9.56 months; and for central hypothyroidism was 15.807±.65 months. Correlation between mean age of diagnosis of thalassemia patients and thyroid hormone dysfunction was non-significant

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Table no.-12 mean + SD of serum ferritin level according Thyroid dysfunctions (n=90)

	Thyroid dysfunctions		
	Normal	Subclinical hypothyroidism	Central hypothyroidism
Mean+SD (ng/ml)	2029.801±163.38	2477.33 ±1062.95	2914.00 9±30.54

Normal V/S Subclinical Hypothyroidism = P > .05 NS
Normal V/S Central Hypothyroidism = P > .05 NS

Subclinical V/S Central Hypothyroidism = P > .05 NS

The mean value of serum ferritin in euthyroid patients was 2029.80±1163.38 ng/ml; for subclinical hypothyroidism was 2477.33±1062.95 ng/ml; for central hypothyroidism was 2914.00±930.54 ng/ml. Correlation between serum ferritin level and thyroid hormone dysfunction was non-significant.

Table no.-13 mean + SD of number of blood transfusions according Thyroid dysfunctions (n=90)

	Thyroid dysfunctions		
	Normal	Subclinical hypothyroidism	Central hypothyroidism
Mean + SD	113.74 + 73.13	123.78 8+1.11	208.60 +41.90

Normal v/s subclinical hypothyroidism = p > .05 NS

Normal v/s central hypothyroidism = p < .001 HS

Subclinical v/s central hypothyroidism = p < .05 S

The mean number of blood transfusions in euthyroid patient was 113.74 + 73.13; for subclinical hypothyroid was 123.78+81.11; for central hypothyroid was 208.60+41.90. Correlation between number of blood transfusion and thyroid dysfunction was significant between subclinical and central hypothyroidism and highly significant between normal and central hypothyroidism.

Table no.-14 distribution of thyroid dysfunctions according to anti-TPO antibody of study subjects (n=90)

Thyroid dysfunctions	Anti-TPO (IU/ml)		Total
	< 28	> 28	
Normal	58(76.32%)	18(23.68%)	76(100%)
Subclinical hypothyroidism	6(66.67%)	3(33.33%)	9(100%)
Central hypothyroidism	5(100 %)	0(0.00%)	5(100%)
Total	69(76.67%)	21(23.33%)	90(100%)

Out of total 90 patients, 69 (76.67%) subjects had anti-TPO antibody level <28 IU/ml out of which 58 (84.06%) subjects were euthyroid, 6 (8.7%) had subclinical hypothyroidism and 5 (7.25%) had central hypothyroidism. Anti-TPO antibody titre was raised (>28 IU/ml) in 21 (23.33%) subjects. Out of these 21 subjects, only 3 (14.29%) had subclinical hypothyroidism and rest 18 (85.71%) subjects had normal thyroid function test.

VI. Discussions

Our study included total 90 subjects with confirmed diagnosis of β-thalassemia major from the age group of 3 to 18 years. Out of total 90 subjects 69 (76.67%) were male and 21 (23.33%) subjects were female. Similar study was conducted by Malik SA Et al (2010) on the 70 cases of β thalassemia, 47 (67%) were male and 23 (33%) female, with an age range of 5-14 years (mean age 7.6 ± 2.5 years) [12].

The mean age for the male patients was 9.07±4.02 years and for female patients, it was 9.09±3.45 years. So, there was no difference in the mean age of the patients in both sexes. The mean age of patients with hypothyroidism was lower than reported in other studies, which may be due to inadequate chelation therapy, chronic anaemia and malnutrition that is commoner in this part of the world [13].

Out of total 90 study cases thyroid function tests were normal in 76 (84.44%) patients. Overt hypothyroidism was not present in any case. 9 (10%) patients had subclinical hypothyroidism. Primary hypothyroidism was not present in any case while secondary (central) hyperthyroidism was present in 5 (5.56%) patients. The endocrine complications of a sample of 3,817 thalassemia major patients from 29 countries are reported by De Sanctis Et al (2004). They found that the prevalence of primary hypothyroidism was 3.2% across these countries [2].in past, in Hashemizadeh H Et al (2012) study, subclinical hypothyroidism was seen in 7% patients. All of them had normal T4 levels with elevated TSH levels, consistent with a diagnosis of subclinical hypothyroidism [14]. Agarwal MB et al (1992) studied 72 transfusion-dependent iron loaded thalassemia patients for thyroid dysfunction. Thyroid failure (hypothyroidism) was documented in 14 patients (19.4%) in their study. Subclinical hypothyroidism characterized by normal T4, and increased TSH was present in 9 patients (12.5%); overt hypothyroidism characterized by decreased T4 and increased TSH was present in 5 patients (6.9%) [15]. Also, a milder form of 'biochemical' thyroid dysfunction (subclinical hypothyroidism) was found to be more prevalent (12.5%) than overt hypofunction (4%) in study done by Athanasios Zervas Et al (2002)[16]. These data indicated progressive slow dysfunction of the thyroid gland with a degree of pituitary insensitivity to the low fT4 level (central component of hypothyroidism) [17]. In the study of Peiman eshragi Et al (2011) hypothyroidism was present in 19 patients (14.6%); 2 primary overt hypothyroidism, 3 secondary hypothyroidism and 14 subclinical hypothyroidism cases were detected. The discrepancy between the different prevalence of hypothyroidism and the presence or absence of the central component can be partially explained by applying different protocols of blood transfusions and iron chelation with variable affection of the thyroid

and pituitary with the excess iron and/or anemia. In addition, genetic variability to the toxic effect of iron on different organs had been documented in thalassemia.

In our study, subclinical hypothyroidism was present in patients in all age groups, while central hypothyroidism was more prevalent in age group of >12 years. This more prevalence of central hypothyroidism with advancing age shows that some chronicity is required in pathogenesis of central hypothyroidism. Malik SA Et al (2010) studied that the frequency of hypothyroidism was significantly higher in elder age group (47%) as compared to younger age group (20%) indicating an increase in the risk of this complication with advancing age [12].

In total 69 male patients selected for our study, 56 (81.15%) patients were normal; 8 (11.59%) males was found to have subclinical hypothyroidism while remaining 5 (7.24%) had central hypothyroidism. Out of total 21 females surprisingly only 1 (4.76%) female patient was affected with hypothyroidism, that too subclinical hypothyroidism. No female was found to be affected with central hypothyroidism. In the study conducted by Sara Ahmed Malik et al (2010) among the 18 hypothyroid patients, there were 11 (23%) males and 7 (30%) females [75]. Thus, there was no significant difference in the frequency of hypothyroidism between boys and girls. In the study done by Peiman Eshragi et al (2011) also there was no relation in hypothyroidism and patients' gender (p=0.36) [18].

In our study, we tried to determine any relation between degree & type of thyroid dysfunction and subjects' serum ferritin levels. The mean serum ferritin levels in subjects with normal thyroid function tests were 2029.80 + 1163.38. In subjects with subclinical hypothyroidism, these were comparatively higher 2477.33 + 1062.95 but P value was not statistically significant. In centrally hypothyroid subjects, mean ferritin levels were even higher 2914.00 + 930.54 but here also P value was not statistically significant. Although serum ferritin levels reflect total iron stores of the body, but in our study we did not find any statistically significant correlation between serum ferritin levels and degree of thyroid dysfunction. Similarly in Athanasios Zervas et al (2002) study, mean ferritin levels in hypothyroid (overt and subclinical) and euthyroid patients were 2707.66 ± 1990.5 mg/l and 2902.9 ± 1977.3 mg/l, respectively (p= 0.61; ns), indicating no correlation between serum ferritin values and thyroid functional status [16]. Also, Peiman Eshragi et al (2011) studied that the absence of the relationship between ferritin and hypothyroidism may be explained by suggesting that the damage of endocrine glands caused by chronic ischemia is more pronounced than that caused by hemosiderosis as a consequence of iron overload. They found that correlation between hypothyroidism and serum ferritin level was not significant (p=0.584). Measurements of the current serum ferritin levels are, however, only informative about the patient's present condition and they cannot reveal tissue siderosis [14]. Similarly, in study of Alireza Abdollah Shamshirsaz et al (2003), there was no significant difference in mean serum ferritin between hypothyroid patients and others [19]. In the study conducted by Agarwal MB et al (1992,) impaired thyroid functions could not be correlated with age, amount of blood transfused, liver dysfunction or degree of iron overload. It is postulated that an inter-play between chronic hypoxia, liver dysfunction and iron overload may be responsible for the thyroid damage. [15]

However, some studies show that there is a significant correlation between serum ferritin level and thyroid status of the thalassemia patients. In Malik SA et al (2010) study,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 (p=0.037) [12]. On the other hand, Nijaguna N et al (2015) stated that even though their study showed increased serum ferritin levels in all children with hypothyroidism, it didn't show any statistically significant difference in mean serum ferritin level between hypothyroid and euthyroid group [20]. Similar observation has been replicated in various previous studies by Cynthia et al, Habeb et al, Rajesh joshi et al and Agarwal et al [15,20,21,22]. There is no doubt that iron overload has important role to play in thyroid and other endocrinal dysfunction in thalassemic patients, non-significant difference in ferritin levels between hypothyroid and euthyroid group suggests that there are other mechanism by which thyroid dysfunction occurs in these children. It also suggests that recent ferritin levels are not a sensitive marker for tissue ferritin deposition. Study done by cynthia et al also couldn't establish association between iron overload and thyroid dysfunction. In addition, multifactorial etiologies from various endocrine abnormalities in thalassemia major, the difference of iron distribution in various organs, and the difference in sensitivity of various endocrine organs to iron accumulation are all possible reasons and they did not find associations between iron overload and thyroid dysfunction [21]. Study done by Agarwal et al also stated that no correlation could be found between iron overload and hypothyroidism. Other factors which could damage the endocrine glands in thalassemia major include chronic hypoxia due to anaemia and liver dysfunction as the metabolism of various hormones is altered once the liver is damaged [15]. Study done by Pirinccoglu et al also showed no correlation between serum ferritin level and thyroid function [10].

So these studies have reported a lack of concordance of ferritin concentrations with the thyroid function status [3,16,19]. This may be, in part, due to the fact that serum ferritin levels increase linearly with the transfusion load up to 100 units of transfused blood, but thereafter, there is no simple relationship between them

[24]. Also, misleading ferritin levels can occur with chronic inflammatory disease as well as vitamin C deficiency [25,26].

In thalassemia major patient it is mainly attributed to regular transfusions. So we determined relation between thyroid dysfunction and number of blood transfusions in our study subjects. We found that mean number of blood transfusions in euthyroid subjects was 113.74+73.13. In sub-clinically hypothyroid patients, it was comparatively higher, that is 123.78+81.11. In subjects with central hypothyroidism it was 208.60+41.90 which was very much raised in comparison to euthyroid and sub-clinically hypothyroid subjects. The difference between euthyroid and centrally hypothyroid patients was statistically highly significant, ($P<0.001$). The difference between subjects with subclinical hypothyroidism and central hypothyroidism was statistically significant, ($P<0.05$). Although no statistically difference was found between subjects with normal thyroid function and subjects with subclinical hyperthyroidism. Ayfer et al (2011) study also showed that there is no correlation between serum ferritin level and thyroid function but a positive correlation between transfusion frequency, an indirect indication of ferritin overload, and hypothyroidism. The absence of the relationship between ferritin and hypothyroidism may be explained by suggesting that the damage of endocrine glands caused by chronic hypoxia is more pronounced than that caused by hemosiderosis as a consequence of the collapse of iron [10].

. Out of total 90 patients, 69 (76.67%) subjects had low anti-TPO antibody levels (<28 IU/ml) in which 58 (84.06%) subjects were euthyroid, 6 (8.7%) had subclinical hypothyroidism and 5 (7.25%) had central hypothyroidism. Anti-TPO antibody titres were raised (>28 IU/ml) in 21 (23.33%) subjects. Out of these 21 subjects only 3 (14.29%) had subclinical hypothyroidism and rest 18 (85.71%) subjects had normal thyroid function test. None of the subject with raised titres had central hypothyroidism. In Peiman Eshragi et al (2011) study, they found that no patient with hypothyroidism had significant serum level of anti-thyroid antibodies [18]. Similarly Athanasioszervas et al (2002) studied that autoimmunity does not seem to be implicated in the pathogenesis of thyroid failure in thalassemic patients, evidenced by the low incidence of positive thyroid auto-antibodies (4.5%) in their study [16].

VII. Conclusion

Hence to conclude, this study gives the baseline database of the prevalence of hypothyroidism in β-thalassemia patients in our centre. Subclinical hypothyroidism is common endocrinal complication in thalassemia patients, even without clinical sign and symptoms of the disease. Hypothyroidism was not correlated with serum ferritin level of the patients but it was related with the number of blood transfusions. So patients might have hypothyroidism despite of controlled serum ferritin level and proper chelation therapy.

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