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Original Article

Thyroid dysfunction in chronically transfused adults with β-thalassemia major

Handan Haydaroglu Sahin[1], Ilkay Dogan[2]

[1]Gaziantep University, Faculty of Medicine Department of Hematology, Gaziantep, Turkey
[2]Gaziantep University, Faculty of Medicine Department of Biostatistics, Gaziantep, Turkey

Abstract

Aim: This study aims to determine the prevalence and severity of thyroid dysfunction in adult β-thalassemia major (BTM) patients and to investigate its relationship with the frequency of transfusions, serum ferritin levels, and adequacy of oral chelation therapy.

Material and Methods: This study included 62 adult patients diagnosed BTM and had been receiving regular blood transfusions for at least 1 year. Iron load was defined as the serum ferritin level. Thyroid dysfunction was categorized as primary hypothyroidism (thyroid-stimulating hormone (TSH)>5.6 mU/L and serum-free thyroxine (FT4)<0.61 ng/dL), subclinical hypothyroidism (Normal FT4 with TSH>5.6 mU/L) or secondary hypothyroidism (FT4<0.61 ng/dL with low or normal TSH). Patients' data was presented retrospectively.

Results: The prevalence of hypothyroidism was 22.6%, and the prevalence of primary hypothyroidism was 14.6%. Mean ferritin levels were determined as 5283.64±2023.95 ug/L, and 1868.67±955.98 ug/L respectively for patients with hypothyroidism, and euthyroidism; and a significant difference was determined between the two groups (p=0.001). Thyroid dysfunction was encountered more frequently in patients receiving four units of blood transfusion per month, and high-dose chelation therapy (both p=0.001). Severity of thyroid dysfunction was determined to have a statistically significant relationship with increased serum TSH, and decreased serum FT4 levels.

Conclusion: This study determined primary hypothyroidism as the most common subtype of thyroid dysfunction. A significant relationship was found between thyroid dysfunction and serum ferritin levels. In view of these data; reducing the incidence of thyroid dysfunction appears to be possible through successful management of iron chelation therapy in patients receiving regular blood transfusions.

Keywords: β-Thalassemia Major; Serum Ferritin Level; Hypothyroidism.

INTRODUCTION

Thalassemia is known as the most common genetic disorder in the world (1). β-thalassemia is a hereditary disease characterized by an increase in hemoglobin F and a deficiency in beta globin chain synthesis, which causes ineffective erythropoiesis. As a result of this condition, repeated blood transfusions are needed to maintain survival in patients (2). However, repeated blood transfusions give rise to various complications. Among these complications are endocrinopathies, which are induced by excess iron accumulation in tissues (3). While common endocrine complications include retarded growth, delayed puberty, and bone disease, less common complications include diabetes mellitus, and hypoparathyroidism (4). Another endocrinopathy that can be encountered in β-thalassemia major (BTM) patients is thyroid dysfunction. The prevalence of thyroid dysfunction ranges widely from low to 60% and results related to the severity of the disease also show variability across different studies. While some studies determine a significantly increased primary hypothyroidism prevalence (5,6); other series report an increase in the prevalence of subclinical hypothyroidism (7,8). Thyroid dysfunction in BTM patients has been mostly investigated by studies that included a limited number of patients and their merit in terms of reflecting the true prevalence is confined. A study done on the Greek population that included a comprehensive patient mass reported the prevalence of thyroid dysfunction as 16.5% across 200 cases. Of these cases, 4% had overt (primary) hypothyroidism, and 12.5% had subclinical hypothyroidism (9). Although the mechanism responsible for the development of thyroid dysfunction has not been completely revealed, excess accumulation of iron in the

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Corresponding Author: Handan Haydaroglu Sahin, Gaziantep University, Faculty of Medicine Department of Hematology, Gaziantep, Turkey, **E-mail**: tezhandan@hotmail.com

gland appears to be the most likely reason, while chronic tissue hypoxia, free radical damage, and organ siderosis are also described as effective factors (10).

Iron load is the most prominent among the parameters that are important in predicting the prognosis for BTM patients. Serum ferritin levels are generally correlated with body iron stores. Although ferritin can be influenced by certain conditions as it is an acute-phase reactant, it still maintains its importance as a reliable and simple parameter in the follow-up of iron load and chelation therapy (11).

This study aims to determine the prevalence and severity of thyroid dysfunction in adult BTM patients and to investigate its relationship with the frequency of transfusions, serum ferritin levels, and adequacy of oral chelation therapy.

MATERIAL and METHODS

The study included 62 adult patients who were diagnosed with BTM based on hemoglobin electrophoresis and genetic analysis and who had been receiving regular blood transfusions (Transfusion frequency 10-15 ml/kg once every 2-4 weeks) at Gaziantep University of Hematology Department between January 2016 and September 2018. Patients who had coexisting systemic diseases that could affect serum ferritin levels, hypothyroidism in their family history, and known thyroid dysfunction were excluded from the study. The demographic characteristics of the patients and their serum-free thyroxine (FT4), thyroid-stimulating hormone (TSH), anti-thyroglobulin (TGA), and anti-thyroid peroxidase (TPO) levels, which had been tested during routine controls in the morning prior to the transfusion were obtained from the patient files and recorded. Iron load was defined as the serum ferritin level. The Biotech ELISA kit was utilized to analyze FT4, TSH, ferritin levels, and Electrochemiluminescence Immunoassay was used to analyze TGA and TPO antibodies of the patients. Thyroid dysfunction was categorized as Overt (Primary) hypothyroidism (TSH>5.6 mU/L and FT4<0.61 ng/dL), subclinical (Compensated) hypothyroidism (Normal FT4 with TSH>5.6 mU/L) or secondary (central) hypothyroidism (FT4<0.61 ng/dL with low or normal TSH), whereas serum ferritin levels were categorized as slightly elevated: 1000-2500 ug/L, moderately elevated: 2501-4000 ug/L, or significantly elevated: >4000 ug/L. Transfusion frequency was classified as 2/4 units per month based on the need demonstrated by the patients; whereas oral chelation therapy with deferasirox was classified under three groups as: low-dose (20 mg/kg), moderate-dose (21-39 mg/kg), or high-dose (40 mg/kg). Patient data were obtained and presented retrospectively. Written consent forms were obtained from the patients included in the study. Gaziantep University Medical Ethics Committee granted ethical approval for this study.

Statistical Analysis

Demographic characteristics and frequency/percentage analysis of BTM patients are presented using descriptive statistical methods. Mean and standard deviation values were computed for continuous variables. Additionally, the t-test was used in the comparison of hematologic data (age, gender, oral chelation, transfusion frequency, and serum ferritin) based on the state of thyroid dysfunction in independent samples. In addition, the chi-square test was utilized to analyze the relationship between certain characteristics of the patients and the state of thyroid dysfunction. Number, percentage, mean, median, and standard deviation values were computed for the data. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) program was used in the analysis of the data.

RESULTS

In total, 62 patients were included in the study, of which 37 were males and 25 were females. The median age of the patients was 27 years (range 18-58 years). Patients in the study series were assigned to two groups with regard to the age variable, based on the mean patient age. The number of patients aged below 30 was 48 (77.4%) and the number of patients aged 30 or above was 14 (22.6%). Patients who required four units of transfusions per month comprised 53.2% (33 patients) of the entire group. Although the majority of the patients were frequently transfused, a significant portion of the patients manifested slightly elevated serum ferritin levels. The number of patients with slightly elevated serum ferritin levels was 37 (59.7%). 13 (21%) patients had moderately elevated serum ferritin levels, whereas 12 (19.3%) had significantly elevated levels. The number of patients that received maximum-dose oral chelation therapy was 19 (30.7%). Normal thyroid hormone levels were observed in 77.4% (48 patients) of the patients. Nine (14.6%) patients were detected to have overt (primary) hypothyroidism, whereas four (6.4%) had subclinical hypothyroidism. Only one patient manifested central (secondary) hypothyroidism (Table 1).

Thyroid antibody tests were negative for all patients. Two patients with subclinical hypothyroidism demonstrated symptoms that could be connected to hypothyroidism (constipation, hair loss, desire for sleep); whereas, two patients with primary hypothyroidism demonstrated hyperlipidemia (elevated triglyceride levels) and one demonstrated bradycardia. Other patients who were detected to have thyroid dysfunction did not show any symptoms. No patients had palpable goiters in thyroid examinations and no pathologies were detected in thyroid ultrasounds.

Patients with primary hypothyroidism demonstrated a mean TSH value of 8.54±3.11 mU/L, and a mean ferritin level of 6223.78±1924 ug/L. Patients who were detected to have primary hypothyroidism had significantly higher serum ferritin levels. Mean ferritin levels of patients with hypothyroidism (overt, subclinical, and secondary) and patients with normal thyroid hormone levels were respectively 5283.64±2023.95 ug/L and 1868.67±955.98 ug/L; and a significant difference was determined between the two groups with regard to the serum ferritin levels (p=0.001). Comparing the group with thyroid dysfunction to the group with normal thyroid hormone levels revealed

higher TSH levels and lower FT4 levels for the group with thyroid function disorder (for thyroid dysfunction group; mean TSH: 7.9±2.87 mU/L, mean FT4: 0.48±0.22 ng/dL; both p=0.001) (Table 2).

Of the patients detected to have thyroid dysfunction, eight were males and six were females. There was not a significant relationship between gender and thyroid dysfunction (p=0.826). A significant difference was determined between age groups with regard to thyroid dysfunction. Thyroid dysfunction was found to be more prevalent among those aged below 30 (p=0.022). While 10 (71.4%) patients with thyroid function disorder were in the group with significantly elevated ferritin levels; four (28.6%) were in the group with moderately elevated levels. Thyroid dysfunction was determined to be more common in patients with serum ferritin levels above 4000 ug/L and patients who received four units of blood per month (both p=0.001). Of the 14 patients detected to have hypothyroidism, 13 were in the group that received 40mg/kg oral chelation due to moderately/significantly elevated serum ferritin levels. Thyroid dysfunction was encountered more commonly in patients who received high-dose chelation therapy (p=0.001). 13 of the patients with hypothyroidism were in the group that received four units of blood per month, all of the 14 patients were in the group with moderately/significantly elevated ferritin levels, and 13 were in the group that received 40 mg/kg oral chelation (Table 3).

Table 1. Clinical Charateristics and Laboratory Data of β-thalassemia major patients

		n=62	n (%)	Thyroid Dysfunction (Present)
Gender	Male	37	59.68	8
	Female	25	40.32	6
Age	<30 years	48	77.42	14
	≥30 years	14	22.58	0
Oral chelation	20 mg/kg	23	37.10	0
	21-39 mg/kg	20	32.26	1
	40 mg/kg	19	30.65	13
Transfusion frequency	2 units per month	29	46.77	1
	4 units per month	33	53.23	13
Ferritin	1000-2500 ug/L	37	59.68	0
	2501-4000 ug/L	13	20.97	4
	>4000 ug/L	12	19.35	10
Thyroid function	TSH>5.6 mU/L, FT4<0.61 ng/dL	9	14.52	
	TSH>5.6 mU/L FT4= N	4	6.45	
	TSH N/, FT4<0.61 ng/dL	1	1.61	
	TSH: N, FT4: N	48	77.42	

TSH= Thyroid-stimulating hormone; FT4= Free thyroxine; N= Normal

Table 2. Comparison of the Laboratory Data and Thyroid hormone profile of β-thalassemia major patients

	Thyroid Dysfunction	N	Mean	Std. Deviation	T	P
Ferritin	Present	14	5283.64	2023.95	8.879	**0.001**
	Absent	48	1868.67	955.98		
TSH	Present	14	7.90	2.87	8.686	**0.001**
	Absent	48	3.13	1.38		
FT4	Present	14	0.48	0.22	-6.082	**0.001**
	Absent	48	0.82	0.17		

TSH= Thyroid-stimulating hormone; FT4= Free thyroxine

Table 3. Comparison of the Clinical Characteristics and Laboratory Data in the Fourteen Patients with Hypothyroidism

		Thyroid Dysfunction				χ^2	P
		Present		Absent			
		Frequency	Percent	Frequency	Percent		
Gender	Male	8	57.14	29	60.42	0.048	0.826
	Female	6	42.86	19	39.58		
Age	<30 years	14	100	34	70.83	5.274	0.022
	≥30 years	0	0	14	29.17		
Oral chelation	20 mg/kg	0	0	23	47.92	33.083	0.001
	21-39 mg/kg	1	7.14	19	39.58		
	40 mg/kg	13	92.86	6	12.50		
Transfusion frequency	2 units per month	1	7.14	28	58.33	11.408	0.001
	4 units per month	13	92.86	20	41.67		
Ferritin	1000-2500 ug/L	0	0	37	77.08	36.626	0.001
	2501-4000 ug/L	4	28.57	9	18.75		
	>4000 ug/L	10	71.43	2	4.17		

DISCUSSION

BTM patients undergo blood transfusions at regular intervals and suboptimal chelation, which are defined as risk factors for iron load. As in all organs, iron accumulates in the interstitium of the thyroid gland and causes thyroid hemosiderosis. This condition results in a progressive deterioration of thyroid function. Thus, early diagnosis and treatment of thyroid dysfunction in adult patients who receive multiple blood transfusions and manifest complications comprises a significant portion of the management of the disease. The aim of this study is to determine the prevalence and types of thyroid dysfunction across adult BTM patients. Moreover; this study aims to investigate the relationship of thyroid dysfunction with the frequency of transfusions, serum ferritin levels, and adequacy of oral chelation therapy.

Studies that investigated the prevalence of thyroid dysfunction in BTM patients produced conflicting results. Perignon F. et al. reported a hypothyroidism prevalence of 19.3% (12), whereas Jensen CE. et al. reported it as 10% (13). Another study determined a hypothyroidism prevalence of 6.3% and reported that serum ferritin levels above 2500 µg/l were connected to a 3.25-fold increase in the prevalence of hypothyroidism (14). In pediatric BTM patients in the Turkish population, the prevalence of primary hypothyroidism was reported as 4.25% and the prevalence of subclinical hypothyroidism was reported as 2.12%. A correlation was determined between serum ferritin levels and endocrine complications (15). A study conducted in Qatar that included 48 pediatric patients determined no cases of thyroid dysfunction in patients aged below 7 years but reported that 35% had developed hypothyroidism over the course of 12 years of follow-up. Serum FT4 levels were reported to decrease progressively throughout the follow-up period (16). Studies on the prevalence of thyroid dysfunction in BTM patients have generally focused on the childhood period. Only a limited number of studies included adult patients as the disease results in mortality due to iron load and related complications. This study included patients aged above 18 years. Overt (primary) hypothyroidism was detected in nine (14.6%) patients and subclinical hypothyroidism was determined in four (6.4%) patients. In accordance with the studies conducted by Magro S. (5) and Zervas A. (9), our study determined a higher prevalence for primary hypothyroidism. The overall prevalence of thyroid dysfunction in our patient population was found as 22.6%. The prevalence found in our study is higher compared to those reported in many other studies. This suggests that additional factors such as the dietary habits observed in our geographical region (seafood containing high amounts of iodine is not preferred for consumption) and lack of iodine in local drinking water/soil contribute to thyroid dysfunction in Thalassemia patients together with the present iron load. In previous studies conducted to determine the epidemiology of hypothyroidism, a relationship was found between iodine deficiency in food/water, and hypothyroidism prevalence in some populations. Kouamé P et al. investigated relationship between iodine concentration in regional drinking water/soil, and prevalence of hypothyroidism in a population of the west Ivory Coast. The results of the study concluded that there was a relationship between prevalence of endemic goiter and the low iodine content of the soil, water and food in the investigated region (17). Similarly, in another study involving 128,442 newborns in Calabria, Italy, a strong association was found between congenital hypothyroidism, and low iodine concentration in drinking water (18). However, in our study, a certain conclusion cannot be reached due to the absence of a healthy control group in the study, and this limits the value of our study. Mean TSH levels were found as 7.90±2.87 mU/L for patients with hypothyroidism, and as 3.13±1.38 mU/L for euthyroid patients, and these levels were significantly higher in hypothyroid patients, resembling the results

reported by Garadah et al. (19). Accordingly, patients with primary hypothyroidism had a mean serum TSH level of TSH 8.54±3.11 mU/L. Serum FT4 levels were also found to be significantly lower in hypothyroid patients, as reported in the study done by Soliman et al. (16). While 14 of the patients included in the study were aged 30 years or older, all patients with hypothyroidism were aged below 30. Although thyroid dysfunction is expected to be encountered at advanced age, it was interestingly more common across younger patients in our patient group, consistent with the study done by Jensen et al. (13). The median age of patients with hypothyroidism was 22 years (range 18-28 years). This may be connected to the decreased need for blood transfusion due to splenectomy in nine of the 14 patients aged above 30 years. 13 patients with thyroid dysfunction had been receiving four units of blood transfusion per month. A positive correlation was determined between frequent blood transfusions and thyroid dysfunction (p=0.001). Although oral chelation therapy is strongly recommended, high serum ferritin levels and related complications continue to maintain their importance for BTM patients. Serum ferritin levels are generally considered to be correlated with body iron store (9). While some studies determined a positive correlation between serum ferritin levels and thyroid dysfunction in BTM patients (13, 19); most studies did not determine a significant relationship (20,21). When mean serum ferritin levels were compared between the hypothyroid patients and euthyroid thalassemia patients in our series, they were found to be significantly higher in the group with thyroid dysfunction. While the mean serum ferritin level was determined as 5283.64±2023.95 ug/L for patients with hypothyroidism, it was determined as 1868.67±955.98 ug/L for patients with normal thyroid function (p=0.001). The results showed that serum ferritin levels can be utilized as a guiding parameter in the follow-up of tissue hemosiderosis, consistent with the study done by Chirico et al. (22) which proved ferritin as a prognostic marker for BTM patients and a predictive factor for progression to thyroid dysfunction.

Our study demonstrated a significant relationship between deterioration of thyroid function and iron load. Results of our study suggest that thyroid hemosiderosis and thyroid dysfunction can be prevented by closely monitoring iron load in patients who receive frequent blood transfusions and making a conversion from chelation therapy when necessary.

CONCLUSION

Consequently, this study showed that thyroid function disorder was among common endocrine complications that could be encountered in adult BTM patients. Primary hypothyroidism was the most common type of thyroid dysfunction. Thyroid dysfunction was determined to have a strong relationship with the frequency of blood transfusions, serum ferritin levels, and iron chelation therapy. The overall prevalence of thyroid dysfunction was 22.6%, and the prevalence of primary hypothyroidism was 14.6%. The expectation of an increased survival in BTM patients causes an increase in the prevalence of complications. It must be remembered that these complications can be prevented by closely monitoring iron load in chronically transfused patients and through successful management iron chelation therapy.

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Handan Haydaroglu Sahin ORCID: 0000-0002-3467-8819
Ilkay Dogan ORCID: 0000-0001-7552-6478

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