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Evaluation of the Thyroid Status and Types of Thyroid Dysfunction in Beta-Thalassemia Major Patients More Than 9 Years of Age in Wassit, Iraq 2020

Ahmed I. Ansaf[1], Safa Faraj[1]*, Hussien A. Abdul-Azziz[2]

[1]Department of Pediatrics, College of Medicine, Wasit University, Al Kut, Wasit, Iraq; [2]Department of Pediatrics, Al-Kut Materntiy and Child Hospital, Kut, Iraq

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***Correspondence:** Safa Faraj, College of Medicine Wasit University, Al Kut, Wasit, Iraq.
E-mail: safaafaraj@uowasit.edu.iq
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Abstract

BACKGROUND: Hypothyroidism (HT) is one of the commonest endocrine complications that can happened in patients with Beta-Thalassemia Major (BTM) above 9 years old which may pass hidden and untreated for years.

AIM: The aim of the study is to evaluate the thyroid status and types of thyroid dysfunction in BTM Patients above 9 years of age.

METHODS: A cross-sectional study was performed on sixty-six randomly selected patients above 12 years of age with BTM in Al-Kut Heriditory Blood Disease Center at Wassit province from March to August 2020. Thyroid function tests were done (thyroid-stimulating hormone, T3, and T4) to detect the thyroid status and identify patients with thyroid dysfunction and determine the type of HT (Primary, central, Subclinical). Data collected include Age, sex, weight, height, serum ferritin, and mean hemoglobin level, type of chelation therapy, dose, compliance, and frequency of blood transfusion, other diseases such as diabetes mellitus, hepatitis C virus, Hepatitis B virus HBV, human immunodeficiency virus, and heart failure were evaluated statistically.

RESULTS: In the studied patients, thirty-one patients (46.96%) found to have HT; (Seven from them (10.6%) had primary HT, Sixteen (24.2%) had subclinical HT and eight (12.1%) had central HT). Twenty-one (67.74%) patients with HT found to have stunted height or short stature (with significant $p = 0.03$) from them 13 (41.9%) had subclinical HT. By Pearson correlation, increasing serum ferritin levels significantly affect in decreasing thyroxin (T4) levels with inverse correlation ($p = 0.0001$), $(r) = -0.45$.

CONCLUSION: In this study, there was a high prevalence of HT in BTM and the subclinical HT is the most common type, signifies the importance for regular screening and close supervision, especially when high ferritin and or short stature are present.

Introduction

The prevalence of Beta Thalassemia Major (BTM) in Iraq is increasing every day, due to high consanguinity marriage with the absence of premarital screen by hemoglobin (Hb) electrophoresis to prevent this lifelong disease with multisystem complications.

This heavily affects the health system as they need lifelong treatment with blood transfusion with expensive chelation therapy to control iron overload in addition to regular monitoring for bone, heart, liver, kidney, brain, and endocrine functions.

The poor compliance for treatment had a great influence on increasing iron overload and its precipitation on different important organs such as the liver, heart, and endocrine organs.

Still patients with Beta-Thalassemia Major suffer from many unrecognized and poorly estimated endocrine complications causing a huge additional mental and physical sequences.

The frequency of hypothyroidism (HT) in Thalassemia patients ranges from 6 to 30% among different countries [1]. In many studies, they show that the lower iron overload markedly decrease HT prevalence and it seems that the prognosis depends on the amount and the duration of iron overload [2], [3].

In spite of The improvement in the survival rate happened after offering regular blood transfusion with oral and subcutaneous iron chelation treatment for all BTM patients; the frequency of endocrine including HT, hypogonadism, Diabetes Mellitus (DM), hypoparathyroidism have increased in long-term survivors [3], [4], [5].

The needs for assessing, early treatment, and identifying the precipitating factors for HT in BTM are important for this lifelong disease.

Thyroid dysfunction could be primary, i.e.,: The damage in the thyroid gland, central i.e: the pituitary gland or hypothalamus is damaged and the secretion of thyroid-stimulating hormone (TSH) is inhibited, and subclinical: when thyroxine levels are within

normal reference but serum TSH levels are mildly elevated [6], [7].

The sequences of HT may lead to many cardiovascular events such as impairment of contraction and relaxation of heart ventricles, decrease heart rate, and increase peripheral vascular resistance. All these, eventually lead to a decrease in cardiac output.

The subclinical HT which usually the most common type, usually affects brain function, development and can cause memory impairment [3], [8].

Patients and Methods

This is a cross-sectional study that was performed on 66 patients with BTM having more than 9 years old randomly selected in Al-Kut Hereditary Blood Disease Center at Wassit province in the south of Iraq. Data collected from patient's files after taking written permission from the center and patients or their parents. This study is done from March to August 2020. The information were collected from patients file including sex, age, height, weight, type of chelation therapy, frequency of transfusion compliance for treatment, presence of other diseases such as DM, Hepatitis B virus, hepatitis C virus, and amenorrhea were evaluated.

Mean Hb level for the last 12 months, serum ferritin level, Thyroid function were (TSH, T3, T4) was measured by enzyme-linked immunosorbent assay through VIDAS machine in the lab of Al-Kut Hereditary Blood Disease Center.

Thyroid function was evaluated depending of standards of kits used in VIDAS:

Grades of HT have been identified as (1,3):

[1]. Primary HT (high TSH, low T4).
[2]. Subclinical HT (high TSH, normal T4).
[3]. Central HT (low or normal TSH, low T4).

Statistical analysis done SPSS 24 software with $p < 0.05$ regarded as significant.

The correlations between Ferritin and the age of the studied patients, ferritin, and thyroxine (T4) level, Age with thyroxine (T4) were evaluated by Pearson Correlation.

Standard Deviation and Mean were used for Age, ferritin, T4, T3, TSH, and Hb level.

Results

The demographic data of sixty-six patients who enrolled in this study are shown in Tables 1 and 2, thirty-two of the patients were male (48.5%), and thirty-four of them were female (51.5%), male-to-female ratio 0.9:1.

Table 1: Descriptive data of the studied patients

Item	No.	Percentage
Gender		
Male	32	48.5
Female	34	51.5
Age group		
≤15	13	19.7
More than 15 year	53	80.3
Iron chelator		
Deferasirox (X-jade)	40	60.6
Deferoxamine (Desferal)	26	39.4
Iron chelator compliance		
Good compliance	40	60.6
Poor compliance	26	39.4
Stature for age		
Normal	23	34.8
Below normal	43	65.2
Ferritin level		
Equal or below 2500 ng/ml	14	21.2
More than 2500 ng/ml	52	78.8

Table 2: Descriptive measurements data of the studied patients

Item	N	Minimum	Maximum	Mean	SD
Age/year	66	13	36	18.86	4.6
Mean Hb g/dl	66	6.2000	10.0	8.5	0.7
Serum ferritin (mean) ng/ml	66	716	12300	5485.12	3260.0
TSH mIU/ml	66	0.1200	60.0	11.06	17.16
T4 mmol/L	66	8.4	146.0	76.152	26.9
T3 mmol/L	66	0.3100	4.8	2.0	0.8

TSH: Thyroid-stimulating hormone, Hb: Hemoglobin.

The mean age of the patients was 18.8 years, more than 80% of the patients more than 15 years of age.

All of the patients were treated with iron chelation therapy. Forty patients (60.6%) of them were treated with Deferasirox (X-jade), 26 patients (39.4%) on Deferoxamine (Desferal), more than 60% of the patients were reported as proper iron chelator compliance. The height of 43 patients (65.2%) in the studied sample was below the normal for their age, while 23 patients (34.8%) had average height.

14 (21.2%) patients had serum ferritin below 2500ng/ml. 52 (78.8%) patients had serum ferritin equal to or more than 2500ng/ml; the mean serum ferritin was 5485.12 ng/dl.

The mean Hb level was 8.5 ± 0.7 g/dl (6.20–10.0g/dl). The mean serum level of TSH was 11.06 mIU/ml with range (0.1200–60.0). The range of the T4 level was between 8.4–146.0 mmol/L, and the mean level was (76.152 mmol/L). The range level of T3 was between 3100-4.8, and, the mean level was 2.0 mmol/L.

Table 3 and Figure 1 shows thyroid status of the patients, HT status was detected in 31 patients, and their percentage was 47% from 66 patients, and they classified into three groups: 16 patients with subclinical HT (24.2%), eight patients with central HT (12.1%), seven patients with primary HT (10.6%). The normal thyroid status was reported in 35 (53.0%) of patients.

Table 3: Thyroid status of the studied patients

Item	Frequency	Percent
Normal	35	53.0
Subclinical hypothyroidism	16	24.2
Central hypothyroidism	8	12.1
Primary hypothyroidism	7	10.6
Total	66	100.0

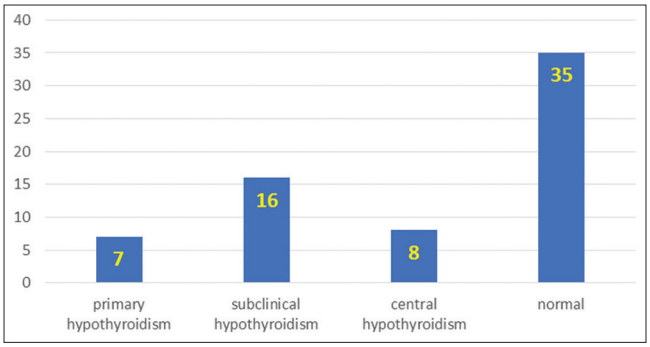

Figure 1: Thyroid status of the patients

Relation between thyroid status and many variables is shown in Table 4; there was a statistically significant correlation between thyroid status and the stature, p = 0.03.

Table 4: Relation between thyroid status of thalassemia patients and other variables

Item	Primary HT	Subclinical HT	Central HT	Normal	Total	p value
Age for stature						
Normal stature	1 (4.3)	3 (13)	6 (26.1)	13 (56.5)	23 (100)	0.031
Below normal	6 (14)	13 (30.2)	2 (4.7)	22 (51.2)	43 (100)	
Serum ferritin						
Equal or below 2500 ng/ml	2 (14.3)	1 (7.1)	4 (28.6)	7 (50)	14 (100)	0.09
More than 2500 ng/ml	5 (9.6)	15 (28.8)	4 (7.7)	28 (53.8)	52 (100)	
Age group						
≤15	2 (15.4)	3 (23.1)	1 (7.7)	7 (53.8)	13 (100)	0.89
more than 15 year	5 (9.4)	13 (24.5)	7 (13.2)	28 (52.8)	53 (100)	

HT: Hypothyroidism.

From 31 patients with HT, twenty one (67.74%) patients had stunted height or short stature, from them 13 (41.9%) had subclinical HT.

Twenty-four patients (46.1%) from fifty-two patients with serum ferritin more than 2500 ng/dl were reported to have HT despite no significant p = 0.09.

Twenty-five (47.1%) from 53 patients with age more than 15 years had HT but with no statistic significant between thyroid status and the age of the patients.

The correlation between the age of the patients and the serum thyroxine T4 level was inverse with p = 0.16, Pearson correlation (r) = –0.17. As showed in Figure 2 (i.e: with increasing in age thyroxin level decrease).

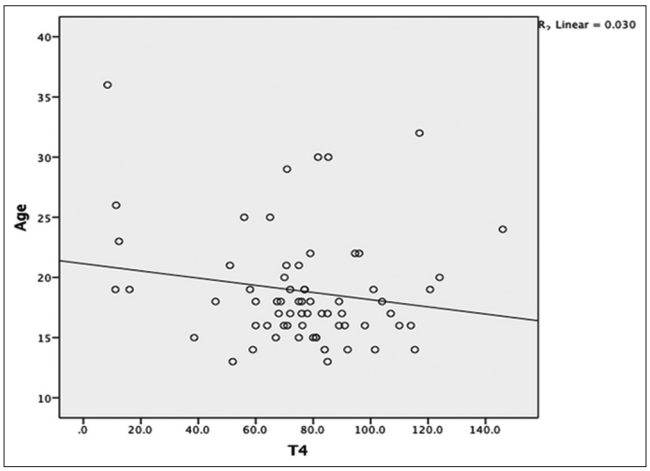

Figure 2: Correlation between age and T4 leve

The correlation between serum ferritin and serum T4 level was inverse with significant p-value, p = 0.0001, Pearson correlation (r) = –0.45. As showed in Figure 3 (i.e.: with increasing serum ferritin thyroxin level decrease).

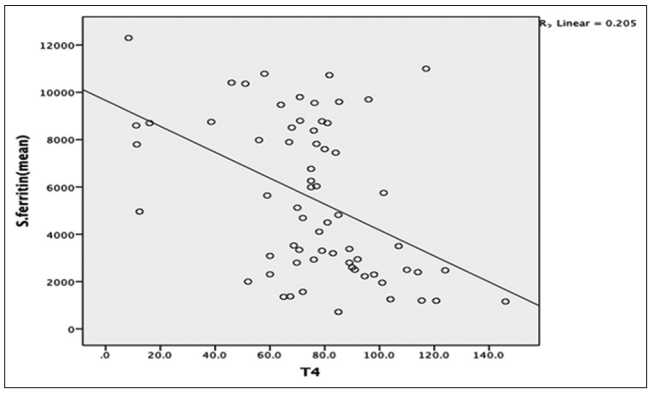

Figure 3: Correlation between serum ferritin and T4 level

Discussion

In this study there was high prevalence of HT (46.96%) among the studied with BTM patients in Wassit province at south of Iraq.

This explanation for unpleasant results is start from absence of primary prevention for this horrible hereditary disease by doing mandatory Hb electrophoresis test for the couple who want to marry. The Hb electrophoresis machine available in the major Wasit province hospitals but not working because there is no maintenance and deficiency for kits needed for its functioning.

Other local causes:

1. Instability in maintenance, availability, and even quality for both chelating agents (Desferal and X- jade) that leads to iron precipitation on vital organs such as the heart, liver, brain, and endocrine organs.
2. Instability in maintenance in biochemical blood tests such as serum ferritin, thyroid function tests, that's needed to be done regularly for early detection which very useful for subclinical HT and required for follow-up after starting hormonal treatment.
3. In many patients, Poverty, low social class are important causes that lead to poor compliance for treatment and follow-up.

Overall, this may indicate a lack of attention with an absence of clear plan for primary prevention by government and health authorities about this inherited blood disease and its related issues and problems which can have lifelong multisystem sequences.

In comparison with other studies, This prevalence was higher than a studies done by Rhman *et al*. (1) in 2019 in Pakistan, HT seen in (29.3%) patients and by Soliman *et al.* in 2013 in Qatar (3) which had (35%) had HT, Jehanzeb *et al*. study in 2016 in Pakistan with (37.5%) have HT, (14.6%) prevalence in Eshragi *et al*. study [9], [10].

In a review article done by Azami *et al*. in 2016, 574 patients had 23.3% overall prevalence [11].

In this study subclinical HT was the most common type (24.6%), this less than Eshragi *et al*. [10], and Malik *et al*. study [12], in Pakistan which had (73.6%), (94.44%) respectively.

However, it is higher than in Soliman study was (6.3%). Other studies done in Iran done for 1151 patients show overall prevalence of 6.7% for subclinical HT in Azami *et al*. review article [11].

The subclinical HT needs more attention for these patients with appropriate therapeutic measures to prevent converting subclinical to overt HT is essential. This include: More strict dose and adherence for iron chelation therapy, financial support, increasing patients and parents education courses, to increase awareness for these complications and its sequences, with regular biochemical and physical monitoring.

In this study (12.1%) had central HT due to decreased secretion of TSH from the anterior pituitary gland or the hypothalamus and this was less than Soliman *et al.* [7], and Eshragi *et al.* studies which have (76.4%) and (15.7%) respectively central HT [10].

In this study primary HT detected in (10.6%) of the studied patients which is similar to Eshragi *et al.* study (10.5%) and less than Malik *et al.* [12], and Soliman [7], studies which both had (5.8%) of primary HT and it is less than Azami *et al.* with 3.6% prevalence of primary HT [11].

In this study, there was a significant relation between short stature or height with HT p = 0.03. From thirty-one patients with HT; Twenty one (67.74%) patients had stunted height or short stature, from them 13 (41.9%) had subclinical HT. This similar to Eshragi *et al.* study which shows significant relation between HT and Height p (0.002) [10].

Strategy of Hypertransfusion with chelation therapy improves the expectancy of life, but the cost, difficulty in administration, and availability make iron or ferritin control is difficult [13].

In this study there was an inverse relation between serum ferritin and serum T4 level with significant p-value, p = 0.0001; which means with increasing ferritin level the chance of finding low thyroxin level will be expected from iron overload infiltration into the thyroid glands with or without pituitary glands involvements, this goes with Malik *et al*. [12], and Jehanzeb *et al*. [9] studies. both found frequency of HT was associated with increased serum ferritin level but this does not go with Eshragi *et al*. study which found no significant relation between ferritin and HT p (0.584) [10].

In Soliman *et al.* study [7], found close to our study result through negative correlation between serum ferritin and FT4 (r = –0.39, p = 0.007).

Iron overload is the Major complication of thalassemia and is the most important concern for management [14].

In this study, the correlation between the age and serum T4 level was inverse relation but with insignificant p = 0.16, Pearson correlation (r) = –0.17.; which means with increasing age of patient with thalassemia Major the level of thyroxin likely to be low or decreased. Azami *et al*. [11], mention endocrine complications more common in the 2nd decades of life in thalassemia Major patients and this close to Soliman study they found FT4 level show progressive decrease over the 12 years of age [7].

More studies are needed and larger sample of included patient to support and modify the possible causes or associated factors.

Conclusions

The prevalence of HT in thalassemia major patients in this study was high in Kut city south of Iraq. Authority planning for primary prevention and close supervision seems to be essential to minimize this inherited blood disease and its multi-system complications including the thyroid dysfunctions with high relation between HT with short stature and high ferritin level.

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