Advanced Medical Journal, Vol.9, No.2, P.128-135, 2024 https://doi.org/10.56056/amj.2024.265

The frequency of clinical and subclinical hypothyroidism in transfusion dependent thalassemia patients in Slemani city /Iraq

Dezheen Jamal Mohammed Rashid* Kawa Muhamad Ameen Nawsherwan Sadiq Mohammed*****

Abstract

Background and objective: Thyroid disorders caused by blood transfusion in thalassemia patients could affect human health and growth, this study was conducted to determine the frequency of clinical and subclinical hypothyroidism in blood transfusion-dependent thalassemia patients in the city of Slemani, Kurdistan Region, Iraq.

Methods: The current study is a retrospective cross-sectional study (comparative analysis) conducted in Slemani center for thalassemia patients and congenital blood, between December 2021 and July 2022. Participants included l07 thalassemia patients with medical records the sampling method was a convenience method. The data was collected through the review of patients' files and blood tests, including(thyroid hormones, hemoglobin level, serum ferritin level), with a questionnaire that was completed through an interview with the patients.

Results: The results of thyroid function tests have shown that 21/107 pateints (19.6%) have hypothyroidism, 6 patients have overt hypothyroidism, and 15 patients have subclinical showed that 23/107 patients and 4/107 patients had hight and low levels,respectively, and there was statistically a significant difference in the average Thyroid stimulating hormone and serum thyroxin levels in two groups of hypothyroid and euthyroid patients and mean ferritine serum level between these two groups was 2166.7±2174.8 and 2068.37±1919.97 respictively ,which was not a statistically significant difference .

Conclusion: Considering the high prevalence of hypothyroidism in thalassemia patients, measuring Thyroid stimulating hormone and thyroxin can be very important and vital in the initial screenings,effective treatment and follow-up of patients.

Keywords: Hypothyroidism, Thyroid Stimulating Hormone (TSH), Transfusion Dependent Thalassemia (TDT), Serum Free Thyroxin (FT4)

Introduction

Thalassemia is a diverse set of hereditary illnesses caused by a reduced production of hemoglobin's alpha or beta chains which leading to anemia that begins in childhood and lasts throughout life. Beta-thalassemia (BTM) is a hereditary mutation of the beta-globin gene that results in a hemoglobin chain with a decreased beta-globin chain.

* MBChB, KHCMS Candidate/ Clinical Hematology. Hiwa Cancer hospital, Slemani, Kurdistan Region,Iraq. E-mail: jdezheen@gmail.com. Corresponding author**MBChB, FRCP, PhD Assistant professor of clinical hematology, Department of Medicine, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region, Iraq. E-mail: mah_kawa@yahoo.com ***MBChB, FIBMS-path, Consultant hematopathologist Department of Pathology, Nanakali hospital, Erbil, Kurdistan Region, Iraq.E-mail: nawsherwan.sadiq@hmu.edu.krd

Over 200 thalassemia-causing mutations in the beta-globin gene have resulted in the disease's vast genotypic and clinical heterogeneity.[1] Clinical and laboratory results distinguish the three types of beta-thalassemia. Beta-thalassemia minor, commonly known as carrier or trait, is a heterozygous status characterized by mild anemia. Beta-thalassemia intermedia and beta-thalassemia major are more severe anemias caused by homozygosity or compound heterozygosity for beta-thalassemia mutations. Transfusion dependency thalassemia (TDT) distinguishes these two clinically. Intermedia does not normally require transfusions, but beta-thalassemia major necessitates.[2] Because BTM is linked with severe anemia and hemoglobin levels below 7 g/dl, blood transfusions are required every 2-5 weeks to maintain a pre-transfusion hemoglobin level over 10 g/dl and lead a normal life.[3] Each unit of red cell concentrate (RCC) includes around 200 milligrams of iron, resulting in iron deposition in numerous organs such as the liver, heart, endocrine glands, and so on.[4] Iron excess affects patients' health and life expectancy; iron chelation treatment (ICT) begins soon after the first year of transfusion.[5] One of the most frequent side effects of iron excess is endocrinopathies.[6,7] After short stature, diabetes mellitus, hypogonadism, osteopenia and osteoporosis, hypothyroidism is one of the most prevalent endocrine diseases affecting 9.2% of patients.[8]An iron deposition is the primary cause of endocrine gland damage, directly or via the hypothalamic-pituitary axis. High ferritin levels, poor chelation compliance, and splenectomy raise the incidence of endocrinopathies in thalassemia patients.[9,10] The clinical effects of excessive iron deposition in the thyroid gland led to impaired thyroid functioning (including subclinical hypothyroidism and secondary hypothyroidism as well as primary hypothyroidism induced by thyroid abnormalities).[11,12] Central Hypothyroidism is rare. Normal blood T4 levels and a slightly elevated TSH level are indicators of subclinical hypothyroidism. It is debatable whether people with subclinical hypothyroidism should be managed.[13] In 35% of the thalassemic patients evaluated by Soliman et al. worsening thyroid function was seen by the age of 18 years. 13/17 (76%) of these individuals did not properly elevate their TSH in response to the low levels of FT4 in the blood, which suggests that a substantial percentage of these patients have an abnormal pituitary thyrotrophic function.[14] Also, the results of Yassouf et al. show that hypothyroidism affects 30.5% of patients with beta-thalassemia major, with subclinical hypothyroidism accounting for the majority of cases at 29.27%,[15]according to these studies and the fact that beta thalassemia major is a major health problem worldwide; it can affect the thyroid gland. Few studies have been conducted on the prevalence and nature of thyroid dysfunction in Iraq. Therefore, this study was conducted to determine the frequency of clinical and subclinical hypothyroidism in blood transfusion-dependent thalassemia patients in Slemani, Kurdistan Region, Iraq.

Patients and methods

The current study is a retrospective cross-sectional study (comparative analysis) conducted in Slemani center for thalassemia patients, between December 2021 and July 2022. The study samples included 107 thalassemia patients**;** the sampling method was a convenience method. The inclusion criteria was patients with a definite diagnosis of thalassemia, and all age groups. Exclusion criteria included bone marrow transplantation during the study and death of patients.

The participant’s data was collected through the review of patients' files, the results of blood tests, including thyroid hormones, hemoglobin level, serum ferritin

level and blood group, and a questionnaire completed through an interview with the patients. After obtaining the necessary permission and approval from the ethical committee of the thalassemia center and the research field managers, all patients' information was obtained from the statistics center. Medical records of the hospital and every patient who came for blood transfusion, the purpose of the study was first explained to the patient and the ethical codes according to the Declaration of Helsinki, data collection was followed. The obtained data were entered into SPSS software version 22, and then descriptive, correlation and chi-square statistical tests were used for analysis, considering a significance level of less than 0.05.

Results

The mean age of 107 studied patients was 20.56±8.84, the youngest was 4 years old, and the oldest was 48 years old. Fifty-nine patients (55.1%) were male. The patients' mean weight was 49.26 ± 15.06, with a range of 13 to 98 kg. The mean height was 152.53 ± 18.01, with a range of 98 to 190 cm. The mean BMI of the patients was 31.45±16.37 kg/m^2. Table (1).

Table (1): Demographic characteristics distribution among 107 blood TDT patient

Variable	Mean±SD	Range	No (%)
Age	20.56±8.84	4-48	
			Gender
Male			59(55.1)
Female			48(44.9)
Weight	49.26±15.06	13.0-98.0	
Height	152.53±18.01	98.0-190.0	
BMI	31.45±16.37	14.58-106.25	

The results showed that 84 patients had an average TSH serum level with a mean of 2.90±1.06, and 23 patients had a high TSH serum level with an average of 7.85±2.60 statistically significant difference (P≤0.001).

Four patients had low T4 serum levels with a mean of 8.7±1.49, and 103 patients had normal T4 serum levels with a mean of 17.25±1.87. Statistically, there was a significant difference between these two groups (P ≤ 0.001) Table (2).

Table (2): Thyroid function status among 107 thalassemic patients

Variable	No (%)	Mean ± SD	Range	p value
				TSH(µIU/ml)
Normal (0.35-4.94)	84(78.5)	2.90±1.06	1-4.9	≤0.001
High (>4.94)	23(21.5)	7.85±2.60	5-14.42	
				Serum FT4 (ng/dl)
Low	4 (3.7)	8.7±1.49	6.6-10.1	≤0.001
Normal	103 (96.3)	17.25±1.87	12-21	

The results of thyroid function tests have shown that 80.4% have euthyroidism and 21 patients (19.6%) have hypothyroidism.

Out of these 21 patients, six patients (%5.6) have overt hypothyroidism, and 15 patients

(%14) have subclinical hypothyroidism Table (3) .

Table (3): Hypothyroidism distribution among blood TDT patients

Thyroid Function Test		NO **(%)**
Euthyroid		86 (80.4)
Hypothyroidism	Overt	6 (5.6)
	Subclinical	15 (14)
Total		107 (100)

The results showed that the mean age of patients with hypothyroidism at the first blood transfusion was 23.57±7.65 months, and this value for euthyroid patients was 19.83±9.0 months, which had a statistically significant difference (P=0.06).Table (4)

The mean number of blood transfusions per year was 2.14±0.79 for hypothyroid patients and 2.17±0.58 for euthyroid patients, which were not statistically significant (P=0.87).

Also, the mean ferritin serum level in the hypothyroid group was 2174.8±2166.7 ng/ml and in the euthyroid group was 1919.97±2068.37 ng/ml, which were not statistically significantly different (P=0.85) Table (4).

The results showed no statistically significant difference between the two groups of patients with hypothyroidism and euthyroid patients in terms of the average value of blood hemoglobin (g/dl) (P=0.6).

There is a statistically significant difference between these two groups regarding the mean values of TSH and T4 levels (P≤0.001). At the same time, there is no statistically significant difference in T3 levels (P=0.72). Table (4).

Table (4): Description of clinical parameters according to thyroid status in 107 patients TDT

Parameter	Hypothyroid Cases (Mean±SD)	Euthyroid Cases (Mean±SD)	p value
Age at First Transfusion/Month	23.57±7.65	19.83±9.0	0.06
No. of Blood Transfusions/Year	2.14±0.79	2.17±0.58	0.87
Serum level of Ferritin ng/ml	2166.7±2174.8	2068.37±1919.97	0.85
Hemoglobin g/dl	3.19±0.60	3.12±0.49	0.60
TSH	7.98±2,58	2.93±1.07	≤0.001
T3	4.77±1.19	4.87±0.92	0.72
T4	14.41±3.35	17.54±1.73	≤0.001

Examining the frequency of hypothyroidism among different ages showed that none of the 11 patients under the age of 10 had hypothyroidism. Out of 40 patients aged 10 to 19 years, 7 had hypothyroidism. 9 out of 39 patients between the ages of 20 and 29 had hypothyroidism. Of 14 patients between 30 and 39, 5 had hypothyroidism. And none of the patients over 40 had hypothyroidism Table (5).

Table (5): Frequency of hypothyroidism among different age groups

Age groups/year	Hypothyroid cases N. (%)	Euthyroid cases N. (%)	Total
≤ 10	0 (0.0)	11 (100.0)	11
10-19	7 (17.5)	33 (82.5)	40
20-29	9 (23.1)	30 (76.9)	39
30-39	5 (35.7)	9 (64.3)	14
≥ 40	0 (0.0)	3 (100.0)	3
Total	21(19.6)	86 (80.4)	107

The correlation test results showed no relationship between serum levels of thyroid hormones and serum ferritin Table (6).

Table (6): Correlation between serum ferritin & thyroid status

parameters		Serum ferritin	TSH	T3	T4
Serum ferritin	Pearson correlation	1	-0.15	-0.191*	-0.221*
	p value		0.88	0.49	0.022
	N	107	107	107	107
*. Correlation is significant at the 0.05 level (2-tailed).					

Discussion

In patients suffering from beta thalassemia major, despite more iron deposition in body tissues and thyroid tissue, thyroid dysfunction in them is mainly limited to subclinical hypothyroidism; In this case, the serum level of thyroxin in the patients is normal, while the secretion of TSH increases, there are no clinical symptoms; in patients who are well treated with iron chelation, hypothyroidism is less common, and the essential way to detect iron is through laboratory tests.

The results have shown that most of the patients have thalassemia major. In the study conducted by Mettananda et al. the results have shown that most of the examined patients are suffering from thalassemia major, whose findings are consistent with the results of the present study.[16]

The results have shown that 80% of people are euthyroid, while nearly 20% of thalassemia patients are hypothyroid. This distribution of hypothyroidism among thalassemia patients is almost consistent with previous studies that investigated the prevalence of hypothyroidism among thalassemia patients and confirmed the results of these studies.[17,18]

Among those with hypothyroidism, we found that 6/21 patients (28%) had overt hypothyroidism and 15 had subclinical hypothyroidism (72%). Compared to the study of Yassouf et al. the number of patients with overt hypothyroidism was

higher in this study,[15] while overt and subclinical hypothyroid cases were consistent with that by Imran et al.[19]

The mean age of hypothyroid patients in the first month of blood transfusion was higher than that of euthyroid patients. This difference in the study by Hamdy et al.[20] and the study by Kadhum et al.[21] and Anafje et al. has also been shown.[22]

In this study, there was no significant difference between hypothyroid and euthyroid patients in mean serum ferritin levels; the same findings were seen by Baul et al.[23]

Examining age groups showed that hypothyroidism was not observed in patients over 40 and below 10 years old. In contrast, in most other studies, hypothyroid patients are observed in the age group below 10 years.[24,25]

In this study, no significant correlation was found between serum ferritin level and thyroid hormones; the reason can be that serum ferritin shows the amount of iron accumulation in the last three months, while the development of glandular disorders requires prolonged contact with iron. The same findings were seen by Sharmin et al.[26] While in the study by Kanbour et al. a significant correlation and relationship between ferritin serum level and thyroid hormones were reported.[27]

Conclusion

Based on the results obtained from this study, significant number of thalassemia patients may face hypothyroidism and has a significant prevalence in different societies. Therefore, more effective treatment and continuous follow-up of these patients to investigate the possibility of hypothyroidism and timely treatment of this condition can be effective in the life expectancy and quality of life.

Conflict of interest:

The authors recorded no conflict of interest.

References

1. Cao A., Galanello R. Beta-thalassemia. Genet Med. 2010;12(2): 61-76.
2. Needs T, Gonzalez-Mosquera LF, Lynch DT. Beta Thalassemia, in StatPearls. StatPearls Publishing LLC.: Treasure Island (FL). 2022,
3. Munice JR H, Campbell J. Alpha and beta thalassemia. Am Fam Physician. 2009 ;80(4):339-44.
4. Islam KA, Azam MS, Mahzabin N, Khan R, Shah MA, Aziz MA. Frequency of Hypothyroidism in Transfusion Dependent Thalassaemia Patients at a Tertiary Care Hospital. Haematology J. Bangladesh. 2020;4(1):16-8.
5. Sanctis VD, Elsedfy H, Soliman AT. et al. Endocrine profile of β-thalassemia major patients followed from childhood to advanced adulthood in a tertiary care center. Indian J Endocrinol Metab. 2016; 20(4):451-9.
6. Sanctis VD, Soliman AT, Yassin MA, et al. Hypogonadism in male thalassemia major patients: pathophysiology, diagnosis and treatment. Acta Biomed.2018; 89(2-s):6-15.
7. Farmaki K., Tzoumari I., Pappa C., Chouliaras G., Berdoukaset V. Normalization of total body iron load with intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol. 2010; 148(3): 466-75.
8. Al-Agha AE., Bawahab NS., Nagadi SA., Alghamdi SA., Felemban DA., Milyani AA. Endocrinopathies complicating transfusion-dependent hemoglobinopathy. Saudi Med J. 2020; 41(2):138–43.
9. Belhoul KM., Bakir ML., Saned MS., Kadhim AM., Musallam KM.,

Taher AT. Serum ferritin levels and endocrinopathy in medically treated patients with β thalassemia major. Ann Hematol.2012;91(7):1107-14.
10. Shalitin S., Carmi D., Weintrob N.et al. Serum ferritin level as a predictor of impaired growth and puberty in thalassemia major patients. Eur J Haematol. 2005; 74(2):93-100.
11. Inati A., Noureldine MA, Mansour A, Abbas HA. Endocrine and Bone Complications in β-Thalassemia Intermedia: Current Understanding and Treatment. Biomed Res Int. 2015; 2015: 813098.
12. Lubis DA., Yunir EM. Endocrinopathies in thalassemia major patient. IOP Conf. Ser.: Earth Environ. Sci. 2018; 125:012174.
13. Rasheed NE, Ahmed SA. Effect of ß-Thalassemia on some Biochemical Parameters. Middle East J. Fam. Med. 2009;7(2): 30-51.
14. Soliman AT, Al Yafei F, Al-Naimi L. et al. Longitudinal study on thyroid function in patients with thalassemia major: High incidence of central hypothyroidism by 18 years. Indian J. Endo. Metab. 2013; 17(6):1090-5.
15. Yassouf MY, Alquobaili F, Kabalan Y, Mukhalalaty Y. Compliance with Deferoxamine Therapy and Thyroid Dysfunction of Patients with β-Thalassemia Major in Syria. Hemoglobin. 2019; 43(3): 218-221.
16. Mettananda S, Pathiraja H, Peiris R. et al. Blood transfusion therapy for β-thalassemia major and hemoglobin E β-thalassemia: Adequacy, trends, and determinants in Sri Lanka. Pediatr. Blood Cancer. 2019;66(5): e27643.
17. Batool T, Irim S, Naeem MM, et al. Hypothyroidism in Children with B-Thalassemia at a Tertiary Hospital of South Punjab, Pakistan. Pak J Med Sci. 2022; 16(07):266-8.
18. Haghpanah S, Bensenjan MH, Sayadi M, et al. The prevalence of Hypothyroidism among patients with β-thalassemia: a systematic review and meta-analysis of cross-sectional studies. Hemoglobin. 2021; 45(5):275-286.
19. Imran A, Wani G, Sing K. Assessment of thyroid profile in children with thalassemia and its correlation with serum ferritin level. Int. J. Med. Health Res. 2018; 4(10):1368.
20. Hamdy M, Draz IH, El Sayed IT, Ayad AA, Salemd MR. Assessment of Quality of Life among Beta-Thalassemia Major Patients Attending the Hematology Outpatient Clinics at Cairo University Hospital. Open Access Maced J Med Sci. 2021; 9(E): 156-60.
21. Kadhum SJ. The prevalence of Hypothyroidism among patients with beta-thalassemia major, Western Iraq. Iraqi Postgrad. Med. J.2018; 17(2):170-5.
22. Anafje M, Jaseb K, Yousefi H. Association Between Serum Ferritin Level and Gene Mutations in Patients with Thalassemia Major and Intermediate. Jundishapur J. Chronic Dis. Care. 2021; 10(1): e110304.
23. Baul, S, Dolai TK, Sahana PK, et al. Does Thyroid dysfunction correlates with iron overload in Eβ thalassemia patients? A study from a tertiary care thalassemia center in India. Archives Med. & Health Sci. 2019; 7(2): 206-11.
24. Iqbal J, Khan KA, Khan ZA, Salman S, Riaz A., Hassan S. Frequency of Hypothyroidism in Beta Thalassemia Patients. Pakistan J. Med. & Health Sci. 2022; 16(7): 52-3.
25. Vincenzo DS, Ashraf TS, Duran C, et al. An ICET-A survey on occult

and emerging endocrine complications in patients with β-thalassemia major: Conclusions and recommendations. Acta Biomed.: Atenei Parmensis. 2018; 89(4): 481-9.
26. Sharmin T, Mollah AH, Morshed AA, Chowdhury MK. Thyroid Status in Children with Transfusion Dependent Hb-E β-Thalassaemia. Mymensingh Med J..2018;27(2): 348-57.
27. Kanbour I, Chandra P, Soliman A et al. Severe liver iron concentrations (LIC) in 24 patients with β-thalassemia major: correlations with the serum ferritin, liver enzymes and endocrine complications. Mediterr. J. Hematol Infect. Dis..2018;10(1): e2018062.