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EVALUATION OF THYROID FUNCTION FOR CHILDREN TRANSFUSION-DEPENDENT THALASSEMIC PATIENTS IN ALMUTHANA CITY IN IRAQ

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Abstract

An inherited hemoglobin problem is thalassemia. In Iraq, where it is seen as a health issue, thalassemia premarital testing is now required. The purpose of this study was to identify the incidence of hypothyroidism and its risk factors among transfusion-dependent individuals. Thalassemic patients were included in an across-sectional investigation that was done in 2021–2022. Thyroid function tests were performed on 61 adult (>14 years) patients, 30 cases, and 31 healthy controls. The initial tests comprised thyroid-stimulating hormone (TSH), free T3, and free T4 levels. Except for two subclinical cases (6.7%), none of the participants in the case group had overt hypothyroidism, while there was no evidence of the condition in the control group. In comparison to the controls, Thalassemic patients are noticeably shorter and lighter (P 0.05). The case's typical hemoglobin level group (8.2) falls well below the typical cutoff threshold of 12 g/dl. The top limit for ferritin is 282ng/ml, whereas the mean ferritin level is 4262ng/ml. The high prevalence of hypothyroidism and associated disorders indicates that individuals are not receiving enough medical care. This emphasizes the need for Thalassemic patients to get close and ongoing monitoring.

Keywords: Thalassemia, thyroid function test ,Iraq

Introduction

Thalassemia is one of the most important genetic hemolytic blood diseases that breaks down red blood cells. the world level in general or the Mediterranean region in particular (1).Thalassemia is a word of Greek origin that means anemia of the Mediterranean region, as the disease was known and widely known in this region and is also known as Mediterranean anemia. anemia, and in the United States of America it was known as Cooleys anemia, relative to the discoverer of the disease who discovered it in 1925 (2,3). The disease spreads in several regions of the world, but it abounds in the following regions:

1- The Mediterranean Basin (Greece, Malta, Cyprus, Turkey, Italy)
2- The Arabian Gulf region
3- The Middle East region, including (Iran, Iraq, Syria, Jordan, Palestine)
4- North Africa, including (Egypt, Tunisia, Algeria, Morocco, Libya, and some other African countries)
5- Southeast Asia, including (Thailand, the Philippines, Indonesia, Singapore, Cambodia, Vietnam, and Malaysia)
6- The proportion of the Indian subcontinent.
7- Other countries (such as China, Armenia, Georgia, Azerbaijan)

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In the Mediterranean region, every newborn born months after birth must undergo this examination to find out if he is pregnant or infected with beta-thalassemia. Either in the Arab Gulf region, every 20 individuals carry this disease, i.e. the percentage of carriers of the disease in the Gulf is 5%, according to statistics. WHO, 8% of the population has thalassemia minor (4,5)

Thalassemia is a genetic disease that affects the making of blood, so the hemoglobin in red blood cells is unable to carry out its function, which causes chronic anemia and signs of disease appear in children in their early stages of life, as a result of receiving two defective genes, one from the father and the other from the mother. Thalassemia is divided into types .The most important of which are, alpha thalassemia and beta thalassemia depending on the location of the defect (6)

It is possible to pass it on to some of the children in its simple form (that is, they become carriers of the disease), but If both parents are carriers of the disease or are infected with it, then there is a 25% chance that a child will be born with a severe form (7,8). As a result, the infected people are divided into two groups:

1. A type in which the person is a carrier of the disease and does not show any symptoms, or he may show symptoms of anemia. In a simple way, he is able to transmit the disease to some of his children.
2. A type in which the person is infected with the disease, and clear symptoms of the disease appear on him from childhood (9)

The gene responsible for the production of alpha globin is called the alpha globin gene and is found on chromosome No. (16) and there are four copies of it (i.e. four genes), two of which are present on chromosome No. (16) that comes from the mother and the other two are present on the chromosome that comes from the mother. B. Any defect in these genes may cause health problems, depending on the number of defective or mutated genes (10).

Types of alpha thalassemia:

1. Silent alpha thlassaemia: If the mutation affects only one gene, the person will not have any health problems.
2. A carrier of alpha thalassemia, if only two of these four inheritors suffer a defect (mutation). He does not suffer from any health problem, but he may have children with health problems in hemoglobin if his wife has the same trait.
3. Heamoglobin h disease: If the defect (mutation) affects three of the four genes, where the child has a decrease in the amount of hemoglobin and it is abnormal, and after some months have passed, the child suffers from anemia of the average type, children do not need blood transfusions, but adults may need transfusions of blood.

Hydro fetal

If all four heirs are damaged, the fetus, while in its mother's womb, will develop severe ascites in the body as a result of severe anemia with heart failure as a secondary result of Hb deficiency in the blood (12). The gene responsible for the production of beta-globin is called the beta-globin gene and is found in the chromosome. No. (11) and there are two of them, one on chromosome

No. (11) coming from the mother and the other on chromosome (11) coming from the father.

Types of beta thalassemia

1- Beta- Thlassaemia –miner : When the beta globin gene is healthy and the other is damaged, this condition is called a carrier of the disease and does not suffer Carriers of the disease from any health problem, except for slight anemia that does not require a blood transfusion (13).
2- Beta- Thlassaemia intermedia It occurs when there is a defect (mutation) in the beta-globin Klamorthy, which results in a moderate-severity deficiency in the amount of beta-globin produced in the body and leads to a moderate-severity deficiency of the Hb level in the blood. The patient does not need periodic blood transfusions.
3- Beta Thlassaemia Major: And it occurs when there is a disease (mutation) in the beta-globin clamor, but the type of defect (mutation) in the beta gene this time is more severe, resulting in a severe decrease in the percentage of beta-globin, thus decreasing Hb as a result of the breakage of abnormal red blood cells before the end of their life span 120 days, and the patient needs periodic blood transfusions every 3-4 weeks to maintain a high percentage of Hb in order for the body to grow healthy (14) Symptoms of thalassemia appear on the patient during the first year of life, and as a result of early red blood cell breakage, severe symptoms of anemia appear as follows the next :-

-Pale skin, sometimes with yellowing
- Delayed growth
-Poor appetite
-Recurrence of infections (15)

With the continuation of anemia, other symptoms appear, such as a change in the shape of the bone, especially the bone .The face, cheeks, and facial features become characteristic of this disease, and an enlarged spleen also occurs And the liver, and the child is delayed in growth, but in simple cases (in carriers of the disease), it may happen Anemia is simple to a degree in which the disease is not clearly visible, and its owner lives very normally and does not need any treatment, and these cases may not be discovered except by chance.

This research aims at the following:

1. Knowing the relationship of some factors to the incidence of thalassemia.
2. Knowing the differences in the infection rate between males and females.

Materials and Methods

Patients and controls

Patients with Thalassemia who need transfusions were chosen at random. Patients were older than 14 and hadn't received a transfusion in the previous two weeks. These requirements were met by 30 patients, and they were enrolled in the study. In addition to the patient group, 31 healthy people were chosen at random from the Iraqi community to serve as the control group. Regarding sex, age range, and geographic dispersion, both groups were matched.

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As stated below, all participants underwent an interview, completed a questionnaire, had their anthropometric measurements taken, and had blood samples obtained. Demographic information, such as age, sex, address, and clinical history, such as the age at first transfusion, frequency of transfusions, chelation therapy, hemoglobin and ferritin levels from the three most recent measurements, menstrual status, and hormone therapy, were also requested. Additionally, the medical records of the patients were examined and compared with the interview results. The TPFS ethics committee accepted the study, and each participant provided their informed permission.

Anthropometric measurements

Anthropometric measurements, height and weight, were taken for cases and controls.
Weight was measured in light clothing and without shoes to the nearest 100 grm using digital scale (Medel crystal-Italy); height was measured (with subjects shoeless) to the nearest 0.1 cm using a drop-down measuring tape. The weight and height for each subject were taken by two health professionals to ensure reliability. Height measuring and weighing tools were calibrated prior to each single measurement by using a standard 5 kg weight; 5 (0.1) and a 100-cm long ruler; 100 (0.1).

Thyroid profiles

Starting at 8:00 am, three blood samples were taken three times from subjects who had been fasting. Sera were immediately separated, evenly pooled, and kept at -80 °C until one batch of analyses was completed. Thyroid-stimulating hormone (TSH), free T3, free T4, and thyroid function were measured. Low FT4 levels and high TSH were the criteria for primary overt hypothyroidism; however, when FT4 and FT3 levels are normal and TSH is raised, the condition is referred to as primary subclinical hypothyroidism.

Statistical analysis

Data are displayed as means and standard deviations. The nonparametric Mann-Whitney test was used to compare variations in group means. The non-parametric model was used to determine the correlations between parameters. Rank-order correlation coefficient for Spearman. Values were compared using Wilcox on signed rank against a fictitious median. The connection was tested using Fischer's exact test. Significant two-tailed p-values were those less than 0.05..

Results

Demography and anthropometry of study population

A total of 61 individuals, 30 transfusion dependent thalassemia patients and 31 healthy human controls were enrolled in the study. The demographic data are summarized in Table 1. The demography in both groups, cases and controls, is comparable.

Table 1. The study subject's demographic and anthropometric data, expressed as a mean (SD)

	Cases	Control	p-value	**Significance**

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				(P<0.05)
Age (year)	20.3	19.1	-	-
Sex Female Male	 17 13	 17 14	-	-
Height (cm)	156.7	166	0.004	S
Weight (kg)	49.6	63.2	0.0005	S

S :significant

As shown in the table 1, the mean height of the thalassemia patients (case group), 156.7 cm is significantly shorter than that of the control group, 166 (P<0.005). Also, the mean weight of the case group participants, 49.6 kg, is significantly lower that of the control group, 63.2 kg (P<0.005). Statistical significance in height and weight between males of the two groups and females of the same groups was also seen (P<0.005).

Table 2. Test results for thyroid profiles in the case and control groups (mean (SD)

Thyroid profile	**Case (n=30)**	**Control (n=30)**	**p-value**	**Significance (p<0.05)**
TSH (mIU/ml)	**3.2**	**1.7**	**0.0001**	**S**
FT3 pg/ml	**2.4**	**2.7**	**0.005**	**S**
FT4 ng/ml	**0.8**	**1.1**	**0.002**	**S**

NS: Not Significant, S: significant

As for the thyroid profile, both FT3 and FT4 are significantly lower in case group while TSH is significantly higher compared to control group , the difference was not significant between ferritin levels and those of gonadal and thyroid profiles (P>0.05). On the other hand, neither cases no controls showed any primary overt hypothyroidism based on test profile. Only two primary subclinical hypothyroidism cases among thalassemia patients were found which showed increased TSH levels and normal levels of FT3 and FT4.

Table 3. Clinical history details (mean (SD)) for case group participants

	Case (n=30)	Cut -off	p-value	Significance **(p<0.05)**
Blood transfusion Age at starting transfusion (year)**	0.4*	-	-	-

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Hb (g/dl)	8.2	12	0.000	S
Chelation therapy				
Patients on therapy, %	53			
Age at starting therapy***	8.2			
Ferritin (ng/ml)	4261	281	0.000	S

* Calculations did not include the five patients who started at 6 years or more

** Date of birth - date of starting transfusion

***Age at diagnosis- Age at starting therapy

The mean hemoglobin level is significantly lower than the hypothetical normal cut-off value (12 g/dl). Approximately half of these patients are not on chelating therapy and even those who are (47%) started at a late age, mean 8.15 years. The mean Ferritin level, the main indicator for monitoring chelating therapy, was significantly higher than the cut-off value which is the upper limit of the ferritin normal range (6.9- 282 ng/ml). As shown in table 3, half of the patients in the case group are transfused once a month and 23% are transfused twice a month. Twenty-five patients started blood transfusion in the first year of life (0.4**)** and five started transfusion when they were 6 years old or more.

Discussion

Additionally, the average hemoglobin level of 8.2 g/dl is much lower than the suggested range of 12 g/dl for females and 13 g/dl for males (16). Our findings indicated poor adherence to chelation therapy, inadequate, irregular, and late beginning, which ultimately led to increased iron overload as seen by elevated serum ferritin levels. Another frequent problem was that thalassemic patients had short stature and were underweight when compared to their normal, healthy peers (P0.05), which is a sign of individuals who have not had adequate blood transfusions (17). This is in line with several investigations, including those by Mostafavi, Najafipour, and Aydinoket who discovered short height in up to 91% of their patients (18,19). Due to growth retardation, which is typical in thalassemic individuals, underweight and short height are caused. The failure of puberty and subsequent growth retardation due to iron overload could be the cause of the chronic anemia brought on by insufficient transfusions, hypoxia, and other endocrine diseases (20,21). The frequency of subclinical hypothyroidism among Palestinian cases was 6.7% compared to zero cases in the control group, despite the fact that hypothyroidism is another prevalent consequence with a range from 0 to 19.4% and even as high as 52% (22,23). The case group had considerably lower FT3 and FT4 values and higher TSH values, pointing to a general propensity toward hypothyroidism. These conflicting data may result from studies that focus on overt hypothyroidism while disregarding subclinical instances and variations in the age groups included in the studies.

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Chelation therapy parameters and chelating agent type, for example, have an impact on hypothyroidism (24,25). Another risk factor for hypothyroidism is the frequency of the transfusion therapy protocol and the consequent iron overload that results from it. Again, and similarly, hypothyroidism shows no significant link with ferritin level (P>0.05), thereby excluding elevated ferritin level as a risk factor (P0.05), which is consistent with other research like Shamshirazet al.'s(26) findings. Both the patients and the controls who took part in the trial had no clinical history of diabetic mellitus (DM). Age, the volume of blood transfused, ferritin levels, compliance with chelation therapy, a family history of DM, and poor pubertal status are some of the variables that affect the prevalence of DM, which ranges from 0% to 24%. About 83% (25/31) of the cases were Thalassemia major in the absence of any genetic testing and based on an early start to blood transfusions (0.4 years), whereas the other 5 instances were Thalassemia intermedia because they started transfusions later. Furthermore, 23% (27,28) of the cases were severe as they were transfused twice per month, and 50% are transfused once per month, both of which are Thalassemia major. If the frequency of blood transfusions represents the severity of the condition, then As their transfusion frequency spans from once a month to once every three months, Thalassemia intermediates are less severe. Even though blood transfusions happen often, anemia is still not appropriately treated.

Poor compliance with chelation therapy (47%) and the relatively late age at start of therapy (8.1 yr) explain the iron overload, which is the main determinant of endocrinopathies and patient survival. Even those on chelation therapy face irregularities, mainly due to inaccessibility of iron chelating medications. Other causes include patients' discomfort and unpunctuality caused by lack of awareness of the consequences of not adhering to chelation therapy. Kidson-Gerber *et al*. mentioned that the use of oral chelation therapy increased rate of compliance.1 Finally, this study showed that patients with blood transfusion frequency of one month or less are not associated with splenectomy(P=0.05) (29,30).

In conclusion, we recommend early (prepubertal), regular, accessible and affordable

Iron chelation therapy and a protocol for early detection and prevention of iron overload which leads to cell damage in various endocrine glands.

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