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Thyroid Dysfunction in Beta-Thalassemia Major: Is It Related to Autoimmunity or Iron Overload?

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ABSTRACT

Purpose: Thyroid dysfunction is an important complication of beta-thalassemia major (β-TM). Iron overload is the most important cause of thyroid dysfunction in this patient group. However, it has been investigated in various studies whether autoimmunity can also cause thyroid dysfunction. This study aimed to determine the frequency of thyroid dysfunction in β-TM and investigate whether the underlying disorder causing thyroid dysfunction is iron overload or autoimmunity.

Methods: This study analyzed 129 patients with β-TM. Free thyroxine (fT4), thyroid-stimulating hormone (TSH), antithyroid peroxidase, antithyroglobulin, and ferritin levels were measured. As the control group, 49 patients who applied to the hospital and requested TSH and fT4 were randomly selected. Both groups were compared in terms of thyroid dysfunction. In the β-TM group, patients with thyroid dysfunction were evaluated for underlying hyperferritinemia and autoimmune susceptibility.

Results: In the β-TM group, overt and subclinical hypothyroidism were detected in 11 (8.5%) and 3 (2.4%) patients, respectively. The ferritin levels of those with hypothyroidism were higher than those with normal thyroid dysfunction ($p = 0.006$, $z = -2.734$). Levels of antithyroid antibodies did not increase in any of the patients with thyroid dysfunction. In the control group, 1 (2%) patient had central hypothyroidism, and 6 (12.2%) had subclinical hypothyroidism. The number of overt hypothyroidism in thalassemia cases was statistically higher than that in the control group ($p = 0.002$).

Conclusion: The results suggest that autoimmunity may not pose a risk factor for the development of hypothyroidism in patients with β-TM, but high ferritin levels may be a reason.

Keywords: Thalassemia major; thyroid disease; autoimmunity; iron overload

Beta-Talasemi Majör hastalarında tiroid disfonksiyonu: Otoimmünite ile mi demir birikimi ile mi ilgili?

ÖZET

Amaç: Beta-talasemi major (β-TM) hastalarında gelişen en önemli komplikasyonlardan biri tiroid disfonksiyonudur. Bu hasta grubunda tiroid disfonksiyonunun en önemli nedeni vücut demir birikimi olarak düşünülmektedir. Ancak otoimmünitenin de tiroid disfonksiyonuna neden olup olmadığı çeşitli çalışmalarda araştırılmıştır. Bu çalışmada, β-TM'de tiroid disfonksiyonu sıklığının belirlenmesi ve tiroid disfonksiyonuna neden olan altta yatan bozukluğun aşırı demir yükü mü yoksa otoimmünite mi olduğunu araştırmak amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmaya, 129 β-TM hastası dahil edildi. Hastaların serbest tiroksin, tiroid stimülan hormon (TSH), anti-tiroid peroksidaz, anti-tiroglobulin ve ferritin seviyeleri ölçüldü. Kontrol grubu olarak, hastaneye herhangi bir nedenle başvurmuş; TSH ve serbest tiroksin seviyeleri istenmiş olan hastalar rastlantısal olarak seçildi. Her iki grup, tiroid disfonksiyonu açısından karşılaştırıldı. Ayrıca β-TM grubundaki hastalar tiroid disfonksiyonuna neden olabilecek hiperferritinemi ve otoimmün yatkınlık açısından araştırıldı.

Bulgular: β-TM grubunda; 11 hastada (%8.5) aşikar, 3 hastada (%2.4) ise subklinik hipotiroidi saptandı. Hipotiroidisi olan hastaların ferritin seviyeleri, hipotiroidisi olmayan hastalara göre anlamlı olarak daha yüksekti ($p=0.006$, $z=-2.734$). Tiroid disfonksiyonu olan hiçbir hastada anti-tiroid antikorlar yükselmemişti. Kontrol grubunda ise bir hastada (%2) santral hipotiroidi, 6 hastada ise (%12.2) subklinik hipotiroidi mevcuttu. Aşikar hipotiroidisi olan hastaların oranı talasemi grubunda, kontrol grubuna göre anlamlı olarak daha yüksek bulundu ($p=0.002$).

Sonuç: Bu çalışmadaki bulgular, β-TM olgularındaki hipotiroidinin nedeninin otoimmün yatkınlıktan çok, hiperferritinemi olduğunu göstermektedir.

Anahtar Kelimeler: Beta-talasemi major, tiroid disfonksiyonu, otoimmünite, demir birikimi

Beta-thalassemia major (β-TM) is a disease that occurs due to a disorder in the hemoglobin synthesis chain, and patients become erythrocyte transfusion-dependent, usually after the sixth month. In Turkey, approximately 5500 patients have thalassemia. It is autosomal recessive; thus, the incidence increases in places where consanguineous marriages are frequent. Therapeutic advances in the management of thalassemia with regular erythrocyte transfusion and iron chelation have extended the life expectancy of these patients. However, chronic anemia and repeated blood transfusions may lead to endocrine complications, such as thyroid dysfunction (1-3).

Although the toxic effect of excess unbound iron in the cell is the main cause of thyroid dysfunction by generating reactive oxygen radicals, many other factors are known, such as chronic hypoxia due to anemia (4-6). In the literature, publications are conflicting regarding the predisposition of patients with thalassemia for autoimmune diseases. The beta-globin gene, which is located in the p15.5 locus of chromosome 11, and immune regulatory genes are located very close to each other; thus, patients with thalassemia minor may have a predisposition for autoimmunity. In addition, the level of hemorphin, which is a protein that suppresses the inflammatory process, decreases with the reduction of the beta-globin chain of hemoglobin, causing a predisposition for autoimmunity (7). Thus, this study aimed to determine the frequency of thyroid dysfunction in β-TM cases and investigate underlying conditions, such as autoimmunity and iron overload, which may cause thyroid impairment.

MATERIAL AND METHODS

Patient Population

This study enrolled 129 patients who had β-TM, aged 6–18 years, and were regularly transfused at the Pediatric Hematology outpatient clinic between May 2016 and May 2017. Informed consent was obtained from the children's legal guardians. The study was performed according to the Helsinki Declaration and was approved by the Harran University Ethics Committee (17/07/12).

Genetic analysis of all of the patients had been performed at the time of diagnosis. They received regular transfusion with erythrocyte suspensions every 2–4 weeks to maintain pre-transfusion hemoglobin levels >9 g/dL. According to their ferritin levels, they were using deferasirox, deferiprone, or a combination of both in different doses as iron chelation treatment. Patients with acute illness or any inflammatory process were excluded from this study. In the control group, 49 patients who applied to the hospital for a routine pediatric examination and were requested thyroid-stimulating hormone (TSH) and free thyroxine (fT4) tests were randomly selected by examining the file records. Both groups were compared in terms of thyroid dysfunction. In the thalassemia major group, patients with thyroid dysfunction were evaluated for the presence of underlying hyperferritinemia and autoimmune susceptibility.

Blood Sample Collection

Before erythrocyte transfusion, blood samples for serum TSH, fT4, antithyroglobulin (anti-TG), antithyroid peroxidase (anti-TPO), and ferritin tests were taken with the other routine tests (complete blood count and biochemistry) on the day of regular admission to the outpatient clinic. The normal values for fT4 and TSH were 0.59–1.7 ng/dL and 0.27–4.2 μIU/L, respectively, according to our laboratory reference range. The positive values for antibodies were accepted as >115 IU/mL for anti-TG and >34 IU/mL for anti-TPO according to our laboratory reference range and the literature (8).

Definitions

Primary hypothyroidism was defined as high TSH levels. It is divided into two:

- Subclinical hypothyroidism: High TSH and normal fT4 levels.
- Overt hypothyroidism: High TSH and low fT4 levels.

Secondary or central hypothyroidism was defined as low TSH and fT4 levels.

Primary hyperthyroidism was defined as low TSH levels. It is divided into two:

- Subclinical hyperthyroidism: Low TSH and normal fT4 levels.
- Overt hyperthyroidism: Low TSH and high fT4 levels.

Secondary or central hyperthyroidism: High TSH and fT4 levels (8,9).

Statistical Analysis

Clinical data were analyzed using IBM SPSS Statistics for Windows version 22 (SPSS Inc., Chicago, IL, USA).

Numerical variables were represented as mean ± standard deviation, and categorical variables were represented as a percentage. The compliance of the variables to normal distribution was examined using the histogram and Kolmogorov–Smirnov test. In comparing two independent groups, the Fisher's exact and Pearson chi-square tests were used for categorical data, and the Mann–Whitney U test was used for continuous variables. The Spearman correlation test was used to evaluate the relationship between continuous variables. Results were evaluated using a 95% confidence interval. P-values of <0.05 showed statistical significance.

RESULTS

This study enrolled 129 (51 female and 78 male) patients with β-TM. The mean patient age was 10.6 ± 3.4 (6–17.8) years. However, the mean age of the control group (n = 49) was 11.3 ± 3.3 years, which ranged from 6 to 18 years, and the female/male ratio was 0.88. No difference was found between the β-TM and control groups concerning age and sex.

In the β-TM group, overt hypothyroidism and subclinical hypothyroidism were detected in 11 (8.5%) and 3 (2.4%) patients, respectively, whereas the other 115 (89.1%) patients had normal thyroid function. Central hypothyroidism and hyperthyroidism were not detected. The mean age of those with hypothyroidism in the β-TM group was 10.9 ± 3.8 (6–17.7) years, and the female/male ratio was 0.55. In the same group, nine of the patients with hypothyroidism were between 6 and 12 years old and five were between 12 and 18 years old (p = 0.842, x2 = 0.04). In the control group, 1 (2%) patient had central hypothyroidism, and 6 (12.2%) had subclinical hypothyroidism. The mean age of those with hypothyroidism in the control group was 11 ± 3.4 (6–16) years, and the female/male ratio was 1.3. No sex difference was found between patients with hypothyroidism in the β-TM and control groups (p = 0.397). The number of overt hypothyroidism in the β-TM group was statistically higher than that in the control group (p = 0.002). The mean TSH and fT4 levels in the β-TM and control groups are demonstrated in Table 1. No difference in TSH levels was found between the β-TM and control groups (p > 0.05, z = –0.013); however, a significant difference in fT4 levels was found (p < 0.001, z = –9.085).

Table 1: Level of TSH and fT4

	Serum TSH (μIU/L)	Serum fT4 (ng/dL)
Thalassemia patients		
All	2.8±2.4 (0.63-13.08)	0.85±0.15 (0.6-1.51)
Subclinical hypothyroidism	4.5±0.14 (4.3-4.6)	1.27±0.08 (1.18-1.34)
Overt hypothyroidism	6.3±2.7 (4.1-13.08)	0.73±0.079 (0.63-0.89)
Normal thyroid function	2.4±0.9 (0.63-6.09)	0.85±0.14 (0.6-1.5)
Control Group		
All	2.7±1.27 (0.6-6.17)	1.25±0.22 (0.1-1.66)
Subclinical hypothyroidism	5.2±0.5 (4.6-6.17)	1.26±0.15 (1.09-1.46)
Normal thyroid function	2.3±0.9 (0.6-4.07)	1.27±0.15 (0.96-1.66)

The mean ferritin level in the β-TM group was 2749 ± 2006 (691–12468) ng/dL, the mean ferritin level of patients with hypothyroidism was 3924 ± 1955 (1581–7220) ng/dL, and those of patients with normal thyroid function was 2606 ± 1973.5 (691.1–12468) ng/dL. A significant difference was found between the ferritin levels of those with and without hypothyroidism (p = 0.006, z = –2.734).

A weak positive linear correlation was found between TSH and ferritin levels in the β-TM group (r = 0.235, p = 0.007); however, no relationship was found between fT4 and ferritin levels (r = –0.151, p = 0.087). In the β-TM group, anti-TPO in 1 (0.8%) patient and anti-TG in 5 (3.9%) patients were high. Thyroid dysfunction was not detected in any of the patients with a positive antithyroid antibody. The mean anti-TG level of the patients was 18.66 ± 35.38 (10–231) IU/mL, and the mean anti-TPO level was 14.04 ± 5.15 (5–34) IU/mL. No difference in anti-TG and anti-TPO levels was found between patients with and without hypothyroidism (p = 0.579 and p = 0.601, respectively). A weakly positive correlation was found between ferritin increase and anti-TG level (p = 0.02, r = 0.204), whereas no significant correlation was found between ferritin levels and anti-TPO levels (p = 0.76, r = 0.157).

DISCUSSION

Early recognition and management of endocrinological complications in patients with thalassemia are one of the important factors affecting the disease course. Hypothyroidism is a common endocrinological complication in this patient group, and its frequency has been reported as 4%–30% in various publications (10,11). In this study, the frequency of primary hypothyroidism was 10.9%, similar to the literature. Subclinical hypothyroidism and overt hypothyroidism constituted 2.4% and 8.5%, respectively, of the primary hypothyroidism group. In addition, the frequency of hypothyroidism was significantly higher in the β-TM group than in the control group. Unlike some other studies, no central hypothyroidism was detected (12,13).

Despite conflicting publications on the relationship between thyroid dysfunction and sex, a higher incidence of subclinical hypothyroidism has been reported in female patients than than males (14). No relationship was found between hypothyroidism and sex. As with all endocrinologic complications, thyroid dysfunction is expected to be more common in older individuals. However, conflicting results have been reported in the literature. For example, in the study conducted by Saleem et al. (15), hypothyroidism was reported as more frequent in the group aged 5–10 years (76.2%) than in the group aged 11–16 years (23.8%). In this study, no difference in the frequency of hypothyroidism was found between the groups aged 6–12 and 12–18 years.

Compared with the general population, patients with thalassemia were thought to have different causes of thyroid disorders. Iron can accumulate in the thyroid gland, pituitary gland, and rarely in the hypothalamus. Compared with other parts of the hypothalamus–pituitary axis, the thyroid gland appears to be more susceptible to iron deposition (16,17). Currently, the most simple and reliable method of measuring body iron accumulation is serum ferritin. In a previous study, patients with a serum ferritin level ≤ 1000 ng/mL were 3.25 times less likely to have hypothyroidism than those with a serum ferritin level >2500 ng/mL (18). In another report, the cut-off ferritin level for the risk of hypothyroidism development was 2000 ng/mL (19). In another study, all children with thyroid impairment had high serum ferritin levels (mean value, 3983 ng/mL); however, no statistical significance was found between thyroid dysfunction and serum ferritin levels (20). In the present study, the mean ferritin level of the patients was 2749 ng/mL; thus, despite intensive chelation therapy recommended for our patients, the poor treatment compliance of patients remains a problem. In this study, the ferritin level of patients with hypothyroidism was higher than those with euthyroidism, and a reasonable relationship was noted between them ($p = 0.006$, $z = -2.734$).

Correlation studies examining the relationship between hyperferritinemia and TSH and fT4 levels were also conducted. Yassouf et al. (11) declared that high serum ferritin levels were directly related to high TSH levels; however, no correlation was found between fT4 and ferritin. In this study, serum ferritin levels correlated with TSH levels ($r = 0.235$, $p = 0.007$), which coincides with the results of Chirico et al. (21).

In the literature, publications on the effects of autoimmunity on thyroid dysfunction in patients with thalassemia are conflicting. In a previous study, the prevalence of autoimmunity was 1.6% in 364 patients with thalassemia, and a limitation of the study was the absence of a control group (22). In a study performed by Zervas et al. (23), antithyroid antibodies were found in 4.5% of patients with thalassemia major, consistent with our findings. In another study, serum ferritin levels were significantly higher in patients with β-TM with positive antithyroid antibodies than in those negative for them, and the authors concluded that iron deposition was responsible for it rather than an autoimmune process of the thyroid gland (24). Interestingly, in another report, antithyroid antibodies in patients with thalassemia were much lower than in those with euthyroidism (9.2% vs 20%), suggesting that iron accumulation may inhibit autoimmunity rather than trigger it (25). In the present study, none of our patients with hypothyroidism had a high antithyroid antibody level. In addition, no significant difference was found between the mean anti-TPO and anti-TG levels in the groups with and without hypothyroidism.

This study had some limitations. In this study, only serum ferritin level was used as an indicator of body iron accumulation. Although ferritin is still the most common parameter used to monitor body iron accumulation in patients with thalassemia, it may not be a sufficient indicator for the hypothalamus–pituitary–thyroid axis. In addition, the number of people in the control group was less than that in the patient group, and parameters related to autoimmunity have not been studied in the control group. Thus, no comparison could be made.

CONCLUSION

In summary, our findings suggest that autoimmunity may not pose a risk for the development of hypothyroidism in patients with β-TM but high ferritin levels may be responsible. Prospective, randomized studies with many patients are needed to associate the relationship between autoimmunity and thyroid dysfunction in β-TM.

DECLARATIONS

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Conflicts of Interest

The authors declare no conflict of interest.

Ethics Approval

The study was approved by the local ethic committee of Harran University (17/07/12).

Availability of Data and Material

The authors verify data transparency.

Authors' Contributions

Conceived and designed the analysis: Burcu Akıncı, Fatma Demir, Ala Üstyol and Deniz Ökdemir

Collected the data : Burcu Akıncı, Fatma Demir, Ala Üstyol and Deniz Ökdemir

Contributed data and analysis tools: Burcu Akıncı, Fatma Demir, Ala Üstyol and Deniz Ökdemir

Performed the analysis: Burcu Akıncı, Ala Üstyol

Wrote the paper: Burcu Akıncı

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