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**CASE REPORT**

# Outcomes of late endocrinologic evaluation in adult patients with thalassemia major: case series

## Talasemi majorlu erişkin hastalarda geç endokrinolojik değerlendirmenin sonuçları: olgu serisi

Emek Topuz[1], Dilek Tüzün[2], Nursel Yurttutan[2], Murat Şahin[2]

[1]Necip Fazıl City Hospital, Kahramanmaraş, Türkiye
[2]Kahramanmaraş Sütçü İmam University, Kahramanmaraş, Türkiye

**Abstract**

Thalassemia is a group of inherited disorders characterized by the reduced or absent synthesis of the globin chains that make up hemoglobin. Transfusion-dependent thalassemia (TDT) is the most severe form, which requires lifelong transfusion. Complications related to the heart, liver and endocrine glands caused by the accumulation of excess iron in different organs due to transfusions are seen in adult patients. Of these complications, endocrine gland complications are widespread in adult patients. Hypogonadism is the most commonly reported endocrine complication, which affects 70-80% of thalassemia major patients. In this case series, we will present three female patients, aged 37, 18 and 27, who were followed up with the diagnosis of TDT and who underwent endocrinological evaluation in adulthood. We aim to emphasize that the diagnosis of hypogonadotropic hypogonadism and growth hormone (GH) deficiency was made late because the endocrinological evaluation of these patients was performed at an adult age, and we discussed the consequences of this. The survival of TDT patients has improved significantly in the last decade due to the introduction of transfusion, oral iron chelation therapies, and bone marrow transplantation, and these patients live into adulthood. Therefore, endocrinologic evaluation should be performed in pre-pubertal and pubertal periods. Early recognition of endocrine complications and early initiation of treatment are important to prevent irreversible sequelae.

**Keywords:**. Transfusion-dependent thalassemia, hypogonadism, growth hormone deficiency

**Öz**

Talasemi, hemoglobinin yapısında bulunan globin zincirlerinin sentezinin azalması veya hiç sentezlenmemesi ile karakterize edilen bir grup kalıtsal hastalıktır. Transfüzyona bağlı talasemi (TDT), yaşam boyu transfüzyon gerektiren en şiddetli formdur. Yetişkin hastalarda, transfüzyonlar nedeniyle farklı organlarda aşırı demir birikimi nedeniyle kalp, karaciğer ve endokrin bezleriyle ilgili komplikasyonlar görülmektedir. Bu komplikasyonlardan özellikle endokrin komplikasyonlar erişkin hastalarda yaygındır. Hipogonadizm ise talasemi majör hastalarının %70-80'ini etkileyen en sık bildirilen endokrin komplikasyondur. Bu olgu serisinde, TDT tanısıyla takip edilen ve ilk olarak erişkin yaşta endokrinolojik değerlendirmeden geçen 37, 18 ve 27 yaşlarındaki üç kadın hastayı sunacağız. Hipogonadotropik hipogonadizm ve büyüme hormonu (GH) eksikliği tanısının, bu hastaların endokrinolojik değerlendirmesi erişkin yaşta yapıldığı için geç tanı konduğunu ve bunun sonuçlarını tartışmayı amaçladık. TDT hastalarının surveyi transfüzyon, oral demir şelasyon tedavilerinin kullanıma girmesi ve kemik iliği nakli gibi tedavi şekillerinin gelişmesi ile son on yılda çok iyileşmiştir.Bu hastalar erişkin döneme kadar yaşamaktadır.Bu nedenle hastalara pre-pubertal ve pubertal dönemde endokrinolojik değerlendirme yapılmalıdır. Endokrin komplikasyonların erken tanınması, erken tedaviye başlanması, geri dönüşümsüz sekelleri önlemek için önemlidir

**Anahtar kelimeler**: Talasemi majör, hipogonadizm,büyüme hormonu eksikliği

Address for Correspondence: Emek Topuz, Endocrinology and Metabolism Specialists, Kahramanmaraş, Necip Fazıl City Hospital Kahramanmaraş, Türkiye E-mail: emektopuz@gmail.com
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## INTRODUCTION

Thalassemia is a group of inherited disorders characterized by the reduced or absent synthesis of the globin chains that make up hemoglobin. The imbalance in alpha and beta globin chain synthesis results in defective erythropoiesis and anemia. TDT is the most severe form, which requires lifelong transfusion[1]. The efficacy of traditional TDT treatment has increased, and the life span of patients has been prolonged with the developments in the field of hematology[2]. Before TDT transfusion applications, it was considered a pediatric disease with short survival and a life span not exceeding the first ten years. In developed countries, the life expectancy of patients receiving treatment has increased to 40-50 years, and life expectancy is expected to extend further. In adult patients, complications related to the heart, liver and endocrine glands are observed due to the accumulation of excess iron in different organs because of transfusions. The most common endocrine complications are growth retardation and delayed puberty, and hypogonadotropic hypogonadism. Other endocrine disorders, such as hypothyroidism, hypoparathyroidism, and diabetes mellitus, are less common in patients with TDT[3]. These complications, especially related to the endocrine glands, are very common in long-lived patients with TDT. Relevant specialists should follow these patients in terms of endocrine complications[3]. D. Santics et al. included 43 adult patients diagnosed with TDT who had been followed up since childhood. They showed that 88.4% of adult TDT patients in this older age group had at least one endocrine complication. The most common endocrine complication is hypogonadotropic hypogonadism[3].

Oguz et al. included 93 adult patients with TDT in the study. The average age of the patients at their first endocrinological examination was determined to be 24 years old, and the most common endocrine complications were osteoporosis and hypogonadism[4].

In this case series, we present three patients with TDT who were diagnosed with hypogonadotropic hypogonadism and GH deficiency late because the initial endocrinologic evaluation was performed in adulthood. We discuss the results of the late endocrinological evaluation in these three cases and emphasize the importance of early detection of pituitary hemochromatosis.

## CASES

### Case 1

A 37-year-old woman has been followed up with a diagnosis of TDT since the age of 2. She regularly receives two units of packed red cells (PRC) replacement every month and uses Deferasirox 10 mg/kg/day for a total of 500 mg/day as iron chelation therapy. She uses L-Thyroxine 100 mg due to primary hypothyroidism. She had her first menstruation at the age of 14. There was hepatosplenomegaly on physical examination. Breast development and pubic hair were evaluated as Tanner stage 5 on physical examination. Her height was measured as 152 cm, and her weight was 50 kg; her mother's height was 160 cm, and her father's height was 176 cm. The target height was calculated as 161 ± 7 cm. Her height was shorter than the target height. When she was 23 years old, she applied to another center due to menstrual irregularity. She was prescribed ethinyl estradiol 0.035 mg + cyproterone acetate 2 mg with the diagnosis of polycystic ovary syndrome, but she did not take it regularly. She has not used it for the last three years. Ten years ago, osteoporosis was diagnosed, and zoledronic acid treatment (IV) was given regularly for six years. The patient stated that she had no menstruation for the last three years, and that is why she applied to us. The patient's laboratory tests are shown in Table 1.

Central GH deficiency and hypogonadotropic hypogonadism were considered with these findings. Since the patient was receiving continuous PRC replacement due to TDT and her hypogonadism started after puberty, it was thought to be secondary to hemochromatosis due to the development of secondary sex characteristics. Pituitary magnetic resonance imaging (MRI) was compatible with hemochromatosis. (Figure 1) Other anterior pituitary hormones were normal. Hormone replacement therapy of the patient was organized as 2 mg estradiol valerate + 0.5 mg norgestrel. Regular menstruation was maintained. The patient with secondary osteoporosis had no history of fracture. Since she had taken bisphosphonate for six years and regular hormone replacement therapy was started,

bisphosphonate treatment was discontinued. Vitamin D and calcium replacement were given. GH therapy could not be given to the patient with GH deficiency whose adult height was shorter than the target height because the epiphyseal lines were closed.

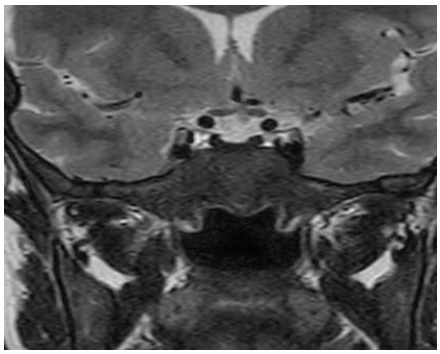

**Figure 1 Pituitary MRI: Hemochromatosis of the pituitary gland (Case 1)**

## Case 2

An 18-year-old female patient has been followed up with a diagnosis of TDT since the age of 2. She regularly receives two units of PRC replacement every month and uses Deferasirox 35 mg/kg/day for a total of 1500 mg/day as iron chelation therapy. She had her first menstruation at the age of 13. There was hepatosplenomegaly on physical examination. Breast development and pubic hair were evaluated as Tanner stage 5 on physical examination. Height was measured as 138 cm, weight was 40 kg, mother's height was 155 cm, and father's height was 165 cm. The target height was calculated as 153 ± 7 cm. Her height was shorter than the target height. She had two years of regular menstruation. She said that she had menstrual irregularity for the last three years, and she had been amenorrheic for the previous year. The patient, who had been amenorrheic for a year, was referred to the endocrinology outpatient clinic for the first time. The patient's laboratory tests are shown in Table 1.

Central GH deficiency and hypogonadotropic hypogonadism were considered with these findings. A 1 mcg ACTH stimulation test was performed on the patient whose basal cortisol was low. It was evaluated as responsive, and central hypocortisolemia was not considered. The patient was evaluated for hypogonadism caused by pituitary hemochromatosis due to TDT and central GH deficiency. Pituitary MRI was compatible with hemochromatosis. (Figure 2) Other anterior pituitary hormones were normal. Hormone replacement therapy was organized as 2 mg estradiol valerate + 0.5 mg norgestrel. The patient with secondary osteoporosis had no history of fracture. She had not received hormone replacement therapy before. Vitamin D was started at a loading dose when vitamin D was found to be 4 ng/ml. Calcium carbonate was added to the treatment at 1000 mg/day. Growth hormone treatment could not be given to the patient with growth hormone deficiency whose adult height was shorter than the target height because the epiphyseal lines were closed.

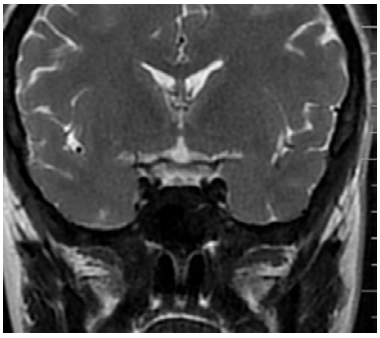

**Figure 2. Pituitary MRI: Hemochromatosis of the pituitary gland (Case 2)**

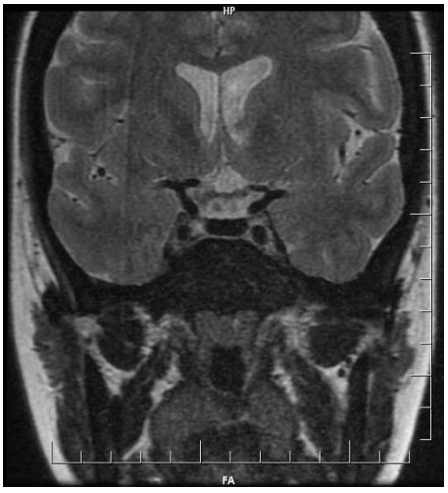


**Figure 3. Pituitary MRI: Hemochromatosis of the pituitary gland (Case 3).**

## Case 3

A 27-year-old woman has been followed up with a diagnosis of TDT since the age of 7. She regularly receives two units of PRC replacement every three weeks and uses Deferasirox 50 mg/kg/day for a total of 2500 mg/day as iron chelation therapy. She had her first menstruation at the age of 15. There was hepatosplenomegaly on physical examination. Breast development and pubic hair were evaluated as Tanner stage 5 on physical examination. Her height was measured as 145 cm., her weight was 50 kg, her mother's height was 156 cm, and her father's height was 168 cm. The target height was calculated as 155 ± 7. Her height was shorter than the target height. A 24-year-old patient who was admitted to an external center because of menstrual irregularity was started on 2 mg estradiol valerate + 0.5 mg norgestrel treatment at the external center. However, she did not take it regularly. She had never used it for the last two years. The patient stated that she had not seen menstruation for the last two years, and that is why she applied to us. The patient's laboratory tests are shown in Table 1.

**Table 1. Laboratory tests**

| Parameters | Case 1 | Case 2 | Case 3 | Reference Values |
|---|---|---|---|---|
| Glucose (mg/dL) | 93 | 80 | 98 | 74-100 |
| Creatinine(mg/dL) | 0.48 | 0,4 | 0,56 | 0.5-0.9 |
| ALT (U/L) | 14 | 14 | 53 | <33 U/L |
| TSH (mIU/L) | 3.15 | 4 | 4 | 0.27-4.2 |
| fT4 (ng/dL) | 1.1 | 1.01 | 1.02 | 0.8-1.9 |
| Cortisol (ug/L) | 11.2 | 3.74 | 12 | 2.47-19 |
| ACTH (ng/L) | 17.3 | 13 | 13 | <46 |
| ACTH(ug/L) stimulation test | | 6/17/23 | | >18 |
| LH (U/L) | 0.5 | 0.35 | 0.86 | 2.4-12.6 |
| FSH (U/L) | 1.3 | 2.48 | 1.18 | 3.5-12.5 |
| Estradiol (ng/L) | <5 | <5 | <5 | 30.9-90.4 |
| GH (ng/mL) | 0.4 | 0.09 | 0.45 | <8 |
| Prolactin (ug/L) | 6.8 | 5.6 | 8.8 | 4.79-23.3 |
| IGF-1 (ug/L) | 33 (109-307) | 60 (73-522) | 98 (101-267) | |
| Hb (g/L) | 8.2 | 8.1 | 9.4 | 11.1-14.7 |
| HCT (%) | 24 | 23 | 27.8 | % 36.9-49.1 |
| Ferritin (ng/mL) | 780 | >1500 | >1500 | 11-306 |
| DEXA | L1-L4<br>T-score:-2.5<br>Z-score:-2.5<br>Femur Neck<br>T-score:-2.4<br>Z-score:-1.9<br>Femur Total<br>T-score:-1.8<br>Z-score: -1.5 | L1-L4<br>T-score:-5.3<br>Z-score:-5.1<br>Femur Neck<br>T-score:-3.9<br>Z-score:-3.1<br>Femur Total<br>T-score:-3.6<br>Z-score -3 | L1-L4<br>T-score:-2.1<br>Z-score:-2.1<br>Femur Neck<br>T-score:-2.1<br>Z-score:-1.9<br>Femur Total<br>T-score:-2.1<br>Z-score: -2 | |

ACTH=Adrenocorticotropic Hormone, TSH=thyroid stimulating hormone, fT4=free thyroxine, LH=luteinizing hormone, FSH=follicle-stimulating hormone, GH: growth hormone,IGF-1: insulin-like growth factor-1,Hb: Hemoglobin, HCT: hematocrit value ALT=alamine aminotransferase, DEXA: Dual-Energy X-ray Absorptiometry

The patient was evaluated for hypogonadism and central GH deficiency caused by pituitary hemochromatosis due to thalassemia major. Pituitary MRI was compatible with hemochromatosis. (Figure 3) Other anterior pituitary hormones were normal. Hormone replacement therapy was adjusted as 2 mg estradiol valerate + 0.5 mg norgestrel. Regular menstruation was ensured. Vitamin D and calcium carbonate 1000 mg/day were added to the treatment. GH treatment could not be given to a patient with GH deficiency whose adult height was shorter than the target height because the epiphyseal lines were closed.

## DISCUSSION

Regular blood transfusion is the primary treatment of TDT patients. Iron chelation therapy is given to prevent endocrinopathies, cardiomyopathy, and chronic liver disease due to iron accumulation because of frequent transfusions. Long-term complications of treatment non-compliance or iron overload occur despite iron chelation therapy in patients with TDT[5].

Iron accumulation in pituitary cells is called pituitary hemochromatosis. Hypogonadism is the most commonly reported endocrine complication, which affects 70-80% of TDT patients. Hypogonadotropic hypogonadism caused by iron accumulation in the pituitary is more common in the etiology of hypogonadism in patients with TDT[6].

The anterior pituitary gland is mainly affected by iron-related free radicals and oxidative stress. Small amounts of iron accumulation detected in the anterior pituitary gland on MRI can cause pituitary insufficiency. Iron accumulation in the anterior pituitary gland begins in the first decade of life. However, clinical signs usually become apparent at the onset of puberty. There is an asymptomatic period of pituitary hemochromatosis before signs of hypogonadism appear. After this asymptomatic period, irreversible damage to the hypothalamic-pituitary-gonadal *(HPG)* axis begins. This irreversible damage causes a marked decrease in spontaneous pulsatile gonadotropin activity and also a decrease in gonadotropin reserve[7].

In recent years, the role of MRI in TDT patients has been investigated. Demonstration of iron accumulation in the pituitary with MRI in the asymptomatic period may be important in early diagnosis. It is difficult to diagnose hypogonadotropic hypogonadism before puberty because of the immaturity of the HPG axis, but pituitary hemochromatosis can be detected early. When hypogonadism develops, it is not possible to completely reverse it with iron chelation[8].

In addition, MRI has been used in studies to estimate iron accumulation in the heart, liver, pancreas and pituitary gland in the asymptomatic period[9].

Reduced pituitary volume has been observed due to apoptosis of gonadotropin-secreting cells associated with hemochromatosis. In patients with iron overload due to frequent transfusions, iron begins to accumulate in the pituitary gland starting in the first decade of life. However, pituitary volume reduction is not observed until the second to third decade of life. Therefore, the appropriate time for MRI imaging was thought to be between 10 and 20 years of age, when pituitary iron accumulates rapidly in many TDT patients[10]. MRI data for children under seven years of age are lacking. Pituitary volume reduction and pituitary height below 4.4 mm have been found to be an independent indicator of hypogonadism[9].

MRI results in studies have shown that patients with moderate to severe pituitary iron overload maintain normal gland volume, which suggests that effective iron chelation therapy can preserve and restore pituitary function[8]. Iron deposition in the anterior pituitary gland significantly reduces signal intensity on pituitary MRI in T2-weighted images and may be instructive for early detection of pituitary hemochromatosis[9].

Pituitary hemochromatosis was seen on pituitary MRI in all three patients we presented. In all three patients, pituitary signal intensity was decreased, and the pituitary gland height was 4.1 mm.

It has been found that serum ferritin levels above 2500 ng/mL during adolescence are a risk factor for the development of hypogonadism, and the risk of developing hypogonadism is 2.75 times higher than patients with serum ferritin levels below 1000 ng/mL[10]. In our cases, the ferritin value of the first patient was 750 ng/mL, and the other two patients had ferritin values above 1500 ng/mL. Other pituitary hormone deficiencies may occur in TDT patients but are less common. The anterior pituitary is especially sensitive to iron-related free radicals and oxidative stress. Therefore, gonadotropes are more commonly affected in TDT patients. Consistent with the literature, hypogonadotropic hypogonadism and central GH deficiency developed in the three patients we presented, and other anterior pituitary hormones were normal.

In the data obtained from seven hospitals in Italy, the percentages of being affected by hypogonadism were found to be almost the same when those born between 1970-1974 and 1975-1979 were compared. Hypogonadism was found to be lower in those born between 1980-1984 compared to the previous years[11]. This suggests that TDT treatment has been

performed better over the years, patient compliance has increased with the use of oral iron chelation therapies and chelation therapies are given more effectively.

A cross-sectional analytic study of 43 patients with TDT conducted in 2016 stated that patients developed endocrine complications in the second decade of life when serum ferritin levels were above 5.000 ng/mL. This was probably due to inadequate iron chelation therapy during the first years of life. 88.4% of adult TDT patients were found to have at least one endocrine complication. In this study, five TDT patients (4 males and one female) aged 10-14 years were treated with standard doses of GH for one year for short stature and GH deficiency. After 12 months of GH treatment, there was an increase in growth rate. Two patients grew 4 cm and more than the previous year; the rest of the patients had a partial response and grew more than 2 cm than the last year[3]. In the three cases we presented, they did not receive GH treatment and did not reach the target height. Case 1 developed GH deficiency despite receiving regular and adequate iron chelation therapy, but Cases 2 and 3 did not receive adequate chelation therapy.

Hypogonadotropic hypogonadism is caused by selective reduction of pituitary gonadotropin function in patients with TDT. In patients with both GH deficiency and hypogonadism, low-dose sex steroid treatment should be considered as an alternative or additional treatment before starting GH treatment[12]. In our three patients, sex steroid treatment was not needed because Tanner stage was 5.

The simpler way to achieve sexual maturation is to use small doses of sex steroids to achieve a good target height. In TDT patients, higher doses are recommended than the doses of GH usually used to accelerate growth[13].

The effectiveness of GH therapy in the treatment of children with TDT who have growth failure due to GH deficiency is controversial. The linear growth rate achieved after GH therapy in children with thalassemia has been reported to be lower than that seen in children with primary GH deficiency due to GH insensitivity[14].

It is not recommended to give GH treatment to support growth in cases where the growth rate drops below 2-2.5 cm per year and the bone age reaches 16-17 years in boys and 14-15 years in girls. It is also stated that the "fusion of epiphyseal growth platelets" corresponds to a bone age of >14 years in girls and >16 years in boys. Additionally, the indication for GH treatment in adults is the diagnosis of severe GH deficiency. Treatment aims to alleviate adverse clinical symptoms, eliminate metabolic disorders associated with GH deficiency, and improve quality of life[15].

An endocrinologic evaluation was not performed in pre-pubertal and puberty periods in all three patients we presented. They could not receive GH treatment for central GH deficiency, and they remained short. Hypogonadotropic hypogonadism was diagnosed late in all three patients, and they did not receive regular sex steroid treatment. Although Case 1 developed osteoporosis, she was not evaluated for hypogonadism and was given bisphosphonate treatment. In Case 1, ferritin was 780 ng/ml, which indicates that the patient received regular iron chelation therapy, but GH deficiency and hypogonadotropic hypogonadism developed.

Oguz et al. included 93 adult patients with TDT between 2014 and 2022. In this study, the average age at the first endocrinologic examination was found to be 24, similar to our cases[4].

Patients may develop hypopituitarism later in life despite long-term iron chelation therapy. Due to the slow accumulation of iron, pituitary insufficiency due to hemochromatosis develops progressively and occurs in advanced ages. In TDT patients, anterior pituitary hormone deficiencies due to hemochromatosis should be kept in mind, and early diagnosis should be made. Endocrine complications related to TDT should be diagnosed at an early stage, and treatment should be initiated early and followed up carefully.

Survival of TDT patients has improved significantly in the last decade with the introduction of transfusion, oral iron chelation therapies and bone marrow transplantation. These patients live into adulthood. Therefore, endocrinologic evaluation should be performed in pre-pubertal and pubertal periods. Early recognition of endocrine complications and early initiation of treatment are important to prevent irreversible sequelae.

In conclusion, endocrine disorders are very common in TDT patients, and iron load in endocrine organs causes them. Early detection of endocrine complications and early endocrinological evaluation can improve a patient's quality of life. It is hoped that these complications will decrease with effective iron chelation treatments in the future.

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**Ethical Approval:** Since this study is a case report, ethics committee approval is not required. Written informed consent was obtained from the patients.
**Peer-review:** Externally peer-reviewed.
**Conflict of Interest:** Authors declared no conflict of interest.
**Financial Disclosure:** Authors declared no financial support
**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.
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