

Case Report

A case of beta thalassemia major increased approach to the treatment by multidisciplinary approach

Beta Talasemi Major Vakası Tedavisinde Artan Multidisipliner Yaklaşım

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ABSTRACT

Beta-thalassemia is a genetic multisystem disease characterized by either absent or decreased beta globin chain production. The most clinically severe form of beta thalassemia is called thalassemia major. The generation of beta-globin is significantly reduced or absent in thalassemia major. Large increases in alpha globin chain synthesis lead to ineffective erythropoiesis. We provide a case of a patient with thalassemia major who developed comorbidities as a result of treatment noncompliance, although they were receiving regular oral iron chelation therapy. The patient in this case study underwent interdisciplinary monitoring and assessment.

Keywords: Neonate, fibromatosis colli, sternocleidomastoid tumor, ultrasonography

ÖZET

Beta-talasemi, beta globin zincirinin üretimini yokluğu ya da azalması ile karakterize edilen genetik multisistemik bir hastalıktır. Beta talaseminin klinik olarak en şiddetli şekline talasemi major denir. Beta globin üretimi talasemi majörde önemli ölçüde azalır veya yoktur. Tedaviye uyumsuzluk nedeniyle komorbiditeler gelişen, düzenli oral demir şelasyon tedavisi alan bir talasemi majör hastasının vakasını sunuyoruz. Hasta, disiplinlerarası izleme ve değerlendirmeye tabi tutuldu.

Keywords: Yenidoğan, fibromatozis kolli, sternocleidomastoid kas tümörü; ultrasonografi

INTRODUCTION

In beta-thalassemia, a hereditary multisystem disease, beta globin chain synthesis is missing or decreased. The most clinically severe type of beta thalassemia is thalassemia major. Beta globin synthesis is severely reduced or absent in thalassemia major. Alpha glo-

bin chain production increases significantly and causes ineffective erythropoiesis. In addition to skeletal deformities, such as enlargement of cranial bones and scoliosis caused by anemia, hepatosplenomegaly and extramedullary hematopoiesis, growth retardation, hy-

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pothyroidism, hypoparathyroidism, gonadal insufficiency and puberty delay, diabetes mellitus, adrenal insufficiency, osteoporosis, and cardiac dysfunction may develop (1,2)

With transfusion and iron chelation therapies, the life expectancy of patients with thalassemia major has been extended to the fourth and fifth decades. However, the extension of life expectancy has led to the emergence of other comorbidities. We present a case who developed comorbidities due to noncompliance with iron chelation therapy while being followed up with the diagnosis of thalassemia major and who was evaluated and followed up with a multidisciplinary approach and treated under regular oral iron chelation therapy. The patient's consent was obtained for this case study.

CASE REPORT

A 23-year-old male patient, who applied to the Pediatric Hematology Oncology outpatient clinic with complaints of growth retardation, walking difficulty for the last year, joint limitation, pain, regression in daily activities, unhappiness and depression had been followed up in our clinic for the last six months.

He was 1 year old, received intermittent blood transfusion for 20 years, and had a splenectomy at the age of eight. His parents were thalassemia carriers, and one sister was diagnosed with thalassemia major. In the genetic analysis of the patient, the c.25_26delAA mutation in HBB (Exon 1,2 Intron 1) was homozygous.

On physical examination, he had a facial appearance typical of thalassemia and short stature (<3 p). Secondary sexual characters were not developed. Somatropin treatment was planned for the 18-year-old patient, whose examination for growth retardation revealed panhypopituitarism and growth hormone deficiency, as his epiphyseal plates were open. However, no response to growth hormone was observed in the 9-month follow-up. Testosterone treatment was started due to hypogonadotropic hypogonadism, as FSH: 0.97 mIU/ml, LH: 0.66 mIU/ml, total testosterone < 7 ng/dl in the tests performed when he was 18 years and 10 months old, but the patient's treatment compliance was not regular for the last four years. In the clinical and laboratory evaluation made by the pediatric endocrinologist, it was seen that the patient did not benefit from testosterone treatment. The patient was administered a dose of the drug that was much lower than the recommended dose at the initiative of the family. The treatment dose was rearranged. Somatropin treat-

ment was discontinued in the patient who reached the final height for bone age. At the age of 19, he was diagnosed with type I diabetes mellitus with diabetic ketoacidosis and had been using insulin for the last four years. Bone densitometry revealed osteoporosis. It was thought that the patient did not comply with his diet and did not pay attention to insulin doses. His peripheral neuropathy may be related to his poorly controlled diabetes.

The pediatric neurology examination showed a significant loss of strength in the upper and lower extremity muscle strength of 4/5 and bilateral ankle dorsiflexion muscle strength of 1/5. There was excessive hip abduction, bilateral sickling gait, and bilateral foot drop. There was significant, widespread paresthesia in the lower extremity. Electromyography revealed left peroneal nerve damage and polyneuropathy in the lower extremity. It was attributed to peripheral neuropathy, not the central nervous system. The patient was taken to a physical therapy and rehabilitation program.

The last echocardiographic evaluation of the patient, followed up with echocardiography and cardiac magnetic resonance (MRI) imaging for cardiac complications, was normal. In the MRI examination performed for iron accumulation in the liver, the T2-value measured with a 1.5 m² ROI from the part of the liver that does not contain gross vascular structure was 2.18 m/s and was compatible with severe iron accumulation.

In the evaluation made by pediatric nephrology, urea, creatinine, uric acid and cystatin C values were within the normal range, and kidney functions were evaluated as normal. Due to the presence of microalbuminuria, diabetic nephropathy was considered by the pediatric nephrologist (24-hour urine protein 4.3 mg/m²/h, microalbumin 326 mg, spot urine albumin/creatinine 109 mg/g) and an ACE inhibitor was started (enalapril 0.05 mg/kg/day).

He had problems complying with treatment and was evaluated by developmental pediatrics using the Vineland Adaptation and Behavior Scale-II. Adaptation level in the field of communication is A (average/between -1 sd and +1 sd), daily living skills BA (below average/between -2 sd and -1 sd), socialization BA (below average/between -2 sd and -1 sd).), movement area L (low) was detected. Internalization problems in maladaptive behaviors were clinically significant, and he was referred to the psychiatric unit.

He had complaints of unhappiness, stagnation, introversion, getting angry easily, not going out, and

difficulty falling asleep after family stressors, health problems and peer bullying for three years. He was evaluated with the diagnosis of Depressive Subtype Adjustment Disorder, and treatment with sertraline 50 mg/day and mirtazapine 15 mg/day was recommended; hereceived 71 points in the Kent EGY test, 79 points in the Porteus Labyrinths and 75 points in total, and was evaluated as Borderline and Mental Retardation. MMPI/SCL-90 was administered on the same date. It was seen that he could not complete the tests and was deemed invalid. During the person's mental status examination, there was a delay in advanced cognitive functions and abstraction skills; his mood was moderately depressive. There were ruminative thoughts about health problems in the thought content, no perception deficits, suicidal homicidal and psychotic findings were detected. It was concluded that it could disrupt the patient's harmony and interpersonal relationships, and that it would be appropriate to follow-up with supportive psychotherapy in the long term.

His ferritin level was 5091 ng/ml when he was 10 years old, he was started on the oral chelator Deferosirox (18 mg/kg/day) due to his noncompliance with the treatment he was using at that time, deferoxamine (20 mg/kg/day) and deferiprone (60mg/kg/day). Afterward, the ferritin level decreased to 4001 ng/ml. However, a year before the diagnosis of diabetes, the patient's ferritin levels were observed to be high. During the period followed by oral chelation therapy, it was observed that the ferritin level decreased to 800 ng/dl, but treatment noncompliance continued (Figure 1). The patient's last ferritin level was 1281 ng/dl while using Deferasirox (16 mg/kg/day).

Our patient was followed up with frequent check-ups in our clinic. It is currently followed with a multidisciplinary approach by the departments of hematology, endocrinology, physical therapy, rehabilitation and psychiatry.

DISCUSSION

Beta thalassemia patients suffer from various degrees of loss of function that may occur in many organs, especially the endocrine system, due to secondary hemochromatosis. Growth retardation, hypothyroidism, hypoparathyroidism, gonadal failure and puberty delay, diabetes mellitus, adrenal insufficiency, osteoporosis, and cardiac dysfunction may develop. (1, 2)

Pituitary dysfunction and hypogonadotropic hypogonadism due to iron accumulation are the most common endocrinological complications despite adequate

chelation therapy. (3-5) In patients with thalassemia, puberty delay and infertility may develop as a result of iron accumulation in the gonadotropic cells of the pituitary gland as a result of transfusions. Additionally, iron accumulation in adipose cells may cause delayed puberty by causing impairment in the synthesis of leptin produced by adipose cells, which serves as a permissive signal to initiate puberty. Detecting iron accumulation in the pituitary gland is crucial because hypogonadism can be reversed with intensive chelation therapy. Low gonadotropin levels occur with significantly high serum iron and ferritin levels. (6) Our patient also had hypogonadism and delayed puberty. Testosterone treatment was started, but due to treatment noncompliance, sufficient effect was not achieved. In patients with thalassemia major, shortening in target height and growth retardation are present in 20-30% of patients. Chronic anemia due to chronic tissue hypoxia, siderosis, bone dysplasia due to chelation toxicity, zinc deficiency, hypothyroidism, hypogonadism/delayed puberty and dysfunction. GHRH-IGF-1 growth axis has been held responsible. (6,7) Treatment was initiated in our patient upon detection of growth hormone deficiency, and treatment was discontinued when the epiphyseal plates were closed.

The prevalence of diabetes in patients with thalassemia varies up to 21%. The main factor that damages pancreatic β -cells and causes diabetes is transfused iron overload. Risk factors for the development of glucose intolerance in thalassemia are older age at the start of chelation therapy, poor compliance with chelation therapy, altered β -cell insulin secretion, insulin resistance following liver disease, autoimmunity, and hepatitis C virus infection that affects glucose. (8) The risk of diabetes can be reduced with serum ferritin below 2500 μ g/L. (9) Our patient developed diabetes mellitus and later diabetic nephropathy at the age of 19 due to noncompliance with treatment. The findings showed that 40-60% of patients with thalassemia have low bone mass (6), and significant osteopenia was detected in our patient. In these patients, endocrine evaluation should be performed regularly, and regular chelate treatment should be started early. 25% of patients with β -thalassemia have neurological symptoms, 22% have neurological neuropathy symptoms, and 53% have pathological values on electromyography. Patients with β -thalassemia have a higher rate of ROS production with subsequent oxidative stress. Free radicals can cause damage to essential macromolecules in the nervous system, resulting in neuronal dysfunction and loss. (10) Peripheral neuropathy is more common in patients with

low hemoglobin levels, high serum ferritin levels, the elderly, and patients with inadequate blood transfusion and iron chelation therapy; this result supports the hypothesis of chronic anemia and iron accumulation as the main risk factors for peripheral neuropathy in thalassemia.(11) Neurological complications in patients with thalassemia have been attributed to various factors, including chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine neurotoxicity.

Current neuropsychological research reveals a very high prevalence of abnormal IQ. These factors include regular school absences due to blood transfusions and frequent hospitalizations, physical and social limitations caused by the disease and its treatment, abnormal mental state resulting from the awareness of being chronically ill, and finally, overprotective family attitudes leading to restricted behavior.(12) In our patient, mental retardation and depression were detected in the psychiatric and developmental pediatrics evaluation. 80% of children diagnosed with thalassemia experience psychological problems, such as depression, emotional problems, somatization, anxiety and behavioral problems.(13) As suggested by health psychology, the cooperation of the patient, his family (the person or people caring for the patient) and healthcare professionals is of great importance to improve the general well-being of people with chronic diseases and to develop healthy coping mechanisms.

Deferasirox film-coated tablet is easier to use than the water-soluble form. By increasing patient compliance, high clinical effectiveness, fewer gastrointestinal side effects, and increased quality of life.(14) Switching from a dispersible tablet to a film-coated tablet formulation of deferasirox improves hemoglobin levels and transfusion interval in patients with transfusion-dependent thalassemia.(15) Our patient compliance increased with the use of deferasirox film-coated tablets and a corresponding decrease in ferritin levels was observed.

CONCLUSION

Patients should be monitored with a multidisciplinary approach. It seems that the most critical point in reducing iron accumulation in patients with thalassemia with regular transfusion and chelation therapy is to increase compliance with treatment. In this way, permanent organ and tissue damage can be prevented in the long term.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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