



Fabry Disease: A Turkish Case with a Novel Mutation and Dermatological Manifestations

Fabry Hastalığı: Yeni Bir Mutasyon ve Cilt Bulgularıyla Seyreden Bir Türk Olgu

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ABSTRACT

Fabry disease is a rare, X-linked disease, caused by the deficiency of lysosomal α -galactosidase. Clinical features are; acroparesthesia, unexplained fever, hypohidrosis and angiokeratomas. Untreated cases die early from cardiac complications, renal insufficiency or stroke. Currently there is no cure for Fabry disease, enzyme replacement therapy is the only choice in this progressive disease. A 9-year-old boy admitted to the Dermatology Clinic with reddish papular skin lesions, joint pain and anhidrosis. Histological examination of the skin biopsy revealed angiokeratoma. There was no renal dysfunction or proteinuria. Biochemical confirmation of Fabry disease was made by determining the deficient leukocyte α -galactosidase activity. Subsequently, the patient's molecular analysis was identified a novel nonsense mutation c. 785G>T in the *GLA* gene. Enzyme replacement therapy with agalsidase beta was started. He is on enzyme replacement therapy for 8 years, significant improvement was obtained in severity and frequency of pain crisis and fatigue. We report this case to emphasize the importance of early diagnosis of Fabry disease restricted to dermatological findings, especially before renal and cardiac involvement occurs, while enzyme replacement therapy is now available. Also this patient is one of the first Fabry patients under enzyme replacement therapy in Turkey.

Key words: Fabry disease, angiokeratoma, enzyme replacement therapy

ÖZET

Fabry hastalığı lizozomal α -galaktosidaz eksikliğine bağlı görülen, X'e bağlı kalıtılan nadir bir hastalıktır. Klinik bulgular; akroparestezi, açıklanamayan ateş, hipohidroz ve anjiyokeratomlardır. Tedavi edilmeyen vakalar erken kardiyak komplikasyonlar, renal yetmezlik veya inme nedeniyle kaybedilirler. Günümüzde Fabry hastalığı için kür bulunmamakla birlikte enzim replasman tedavisi, bu ilerleyici hastalık için tek seçenektir. 9 yaşındaki erkek olgu Dermatoloji kliniğine kırmızı papüller cilt lezyonları, eklem ağrısı ve anhidrozla başvurmuştur. Cilt biyopsisinin histolojik incelemesi anjiyokeratom ile uyumlu bulunmuştur. Renal disfonksiyon veya proteinüri saptanmadı. Fabry hastalığının biyokimyasal doğrulaması lökosit α -galaktosidaz eksikliğinin gösterilmesiyle yapıldı. Daha sonra da, hastanın moleküler incelemesiyle *GLA* geninde c. 785G>T tanımlanmamış mutasyonunu saptandı. 8 yıldır enzim replasman tedavisi altında izlenen hastanın halsizlik yakınmasında ve ağrı ataklarının ciddiyeti ve sıklığında belirgin iyileşme gözlemlendi. Bu hastayı, enzim replasman tedavisinin mümkün olduğu günümüzde, renal ve kardiyak bulgular ortaya çıkmadan sadece cilt bulguları varlığında konulan erken Fabry hastalığı tanısının önemini vurgulamak amacıyla sunduk. Ayrıca bu hasta Türkiye'de enzim replasman tedavisi uygulanan ilk olgulardan biridir.

Anahtar kelimeler: Fabry hastalığı, anjiyokeratom, enzim replasman tedavisi

INTRODUCTION

Anderson-Fabry disease (AFD) is an inborn error of metabolism caused by a genetic defect in the GLA gene, located in the Xq22 region of the X chromosome, which encodes the lysosomal enzyme alpha-galactosidase A¹. AFD is one of the most important sphingolipidoses and it is considered a rare disease, the estimated incidence of AFD is 1 in 117,000 in the general population and 1 in 40,000 in males, primarily affecting hemizygous males and heterozygous females².

Alpha galactosidase A enzyme deficiency leads to the systemic accumulation of globotriaosylceramide (Gb3, also known as ceramide trihexoside) and related glycosphingolipids, inside lysosomes of vascular endothelial cells, renal and myocardial cells, and cells of the autonomic nervous system³. The signs and symptoms emerge solely in childhood and adolescence, beginning with episodes of neuropathic pain and the appearance of angiokeratomas⁴. The incidence of cardiac involvement, renal dysfunction, and cerebrovascular problems increases with age and is the source of major morbidity and mortality^{5,6}.

Biochemical diagnosis of AFD is made by measuring the alpha -Gal A activity in peripheral leucocytes or plasma and genetic confirmation is achieved by alpha -Gal A gene (GLA) sequencing⁷.

AFD can be effectively and safely treated with enzyme replacement therapy (ERT) since 2001, allowing a variety of clinical benefits, including improved renal pathology/function and cardiac function⁸. So it is important to diagnose early in the patient the disease and start the therapy, in order to prevent the progression of the disease⁹.

In this report, we report a 9 year old boy who were diagnosed based on the presence of angiokeratomas alone, without any complaint of pain. We would like to emphasize the importance of early diagnosis of AFD in order to start ERT earlier to prevent rapid disease progression.

CASE

A 9-year-old boy admitted to the Dermatology Clinic with a 2 years history of small, raised, reddish-purple maculopapules affecting his four extremities (Figure 1). He was also complaining about disabling joint pain which is responsive to paracetamol. He tended to suffer from hypohidrosis when feeling hot, and in summer he often had a raised body temperature.

He was born at term after an uneventful pregnancy. Mental and motor developmental milestones were normal. His parents are second degree cousins. He has two healthy sisters. There was no family history for kidney failure, heart disease, stroke or any other inherited metabolic diseases.

On physical examination his weight was 28.5kg (25-50p), his height was 132cm (25-50p). He had no dysmorphic features. His physical examination was normal except for the dermatological findings. Systemic evaluation was normal except dermatological findings. Mental and motor development was normal and did not have any neurological deficits. The dermatologist detected small, raised, reddish-purple maculopapules on his four extremities and hyperkeratotic, hyperpigmented pinpoint macules on the buttocks (Figure 2).

Biochemical and hematological tests were totally normal. Renal function panel, including glomerular filtration rate and urine microalbumin, were normal. Hepatic function tests were also normal. Electrocardiography and echography also showed normal cardiac chamber size and wall thickness. Neurological examination and cerebral magnetic resonance imaging were normal. In addition there were no aneurysmal dilatations of the vessels or corneal verticillata on ophthalmologic investigation.

Hystological examination of one of the cutaneous lesions of the extremities revealed a moderate hyperkeratosis with dilated blood vessels

filled with erythrocytes in the epidermis. Lymphohistiocytic infiltration was also observed. These findings confirmed the diagnosis of angiokeratoma.

The symptoms joint pain and hypohidrosis and angiokeratomas detected on the extremities suggested the diagnosis of AFD. Diagnosis of AFD was based on enzymatic deficiency (alpha galactosidase A enzyme activity: 0nmol/h/ml) and the diagnosis was confirmed with the detection of a novel c. 785G>T nonsense mutation in the *GLA* gene on chromosome Xq22 by sequence analysis. This mutation leads to an aminoacid change at position 262 of the protein (p. Trp262Leu).



Figure 1.



Figure 2.

DISCUSSION

AFD, an X linked lysosomal storage disease caused by the deficiency of alpha galactosidase A, is difficult to diagnose in childhood and early adolescence due to the nonspecific symptoms and findings. Most of the cases are diagnosed lately, usually in adulthood. AFD has a wide range of clinical symptoms including pain and paresthesias in the extremities, angiokeratoma, corneal and lenticular opacities, hypohidrosis, gastrointestinal, cardiac and renal dysfunction¹⁰. Also sensorineural hearing loss, tinnitus and vertigo were observed in these patients¹¹.

Angiokeratoma is considered the cutaneous hallmark of AFD and 66% of male and 36% of female Fabry patients exhibit at least one angiokeratoma during the course of the disease¹². In this case study, we report a 9 year old boy with

Enzyme replacement therapy (ERT) was started with agalsidase beta dose of 1mg/kg body weight every two weeks with an intravenous infusion (IV). He has been on this therapy for 8 years without any complications. Significant improvement was reported in severity and frequency of the pain attacks. There were no significant beneficial effects on angiokeratomas. But new angiokeratomas were not observed. The patient's hypohidrosis also did not improve. Neither a decline in glomerular filtration rate nor proteinuria was detected during the follow-up. Cardiac functions were also stable. There was not any corneal deposition detected by the ophthalmologic slit-lamp microscopy.

AFD, who were diagnosed after angiokeratomas were identified and impaired ability to sweat were learned. Although he was examined by different physicians (dermatologists and pediatricians) he could not have diagnosed for two years. Whereas early diagnose of AFD is important before life-threatening complications occur, AFD should be considered even if a solitary angiokeratoma is the only presenting feature. As in this case, ERT after diagnosis is very beneficial for other systems such as renal, cardiac and neurologic systems.

A presumed diagnosis of AFD can be reached by the demonstration of markedly deficient α -Gal A activity in plasma, isolated leukocytes, and/or cultured cells¹³. Furthermore a detected *GLA* gene mutation is critical for confirmation of AFD¹⁴. In our patient, enzyme activity was zero, and c. 785G>T

mutation was observed; AFD was diagnosed by this nonsense mutation.

Nonsense c.785G>T mutation in the *GLA* gene leads to an aminoacid change at position 262 of the protein (p.Trp262Leu) and was not described before. The physicochemical difference between Tryptophane and Leucine is small (Grantham distance: 61). Trp262 is highly conserved between species (up to *C. elegans*) and with the related protein the lysosomal alpha-galactosidase A. This is a novel mutation and was not found in other Fabry patients.

After the diagnosis, ERT was started with agalsidase beta with a dose of 1mg/kg body weight every two weeks with an intravenous infusion (IV). We evaluated the efficacy of ERT started in the relatively early stages of the disease for 4 years. The treatment was generally well tolerated and infusion-associated reactions were not observed.

However, Fauchais et al. reported that ERT was effective on angiokeratomas, in our patient ERT was not effective at improvement angiokeratomas¹⁵. On the other hand new angiokeratomas has not observed yet.

Our patient had joint pain for years, after the initiation of ERT, severity and frequency of the pain attacks decreased. Similar to this pain outcomes are reported to be improved by ERT in many clinical studies¹⁶.

During the follow-up renal and cardiac functions of our patient were stable under the ERT. With regard to the renal and cardiac manifestations of AFD, early initiation of treatment is expected to provide a better outcome¹⁷.

Although further follow up and more studies are needed to observe the long-term effects of ERT, early initiation of therapy should have been improved the outcome of the disease and prevented end organ damage.

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