Retrospective Evaluation of Clinical and Molecular Characteristics of Patients with Fabry Disease Being Followed-Up in Our Clinic

Kliniğimizde Takip Edilen Fabry Hastalarının Moleküler ve Klinik Özelliklerinin Geriye Dönük Olarak İncelenmesi

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ABSTRACT

Objective: Fabry disease (FD) is an X-linked lysosomal storage disease (LSD), that occurs due to deficient activity of the enzyme alpha-galactosidase A (a-GalA) with multisystemic involvement. The disease can present with a wide range of symptoms, from mild form to the severely affected classical male phenotype with early organ failure and associated morbidity and mortality.

Material and Methods: Patients diagnosed with FD at Dr. Sami Ulus Maternity and Child Health Training and Research Hospital were enrolled. Phenotypic and genotypic presentations of 10 cases from three unrelated families have been evaluated. Diagnoses of relatives of index patients were reached by family screening. Clinical, laboratory and molecular genetic analysis of patients were collected.

Results: A total of 10 patients including 7 males, (mean age 31.8, range: 14-59 years) and 3 females, (mean age 44.6, range: 40-51 years) were evaluated. Various multisystem manifestations were observed, including cardiac, neurological, cerebrovascular and ophtalmological involvement. Eight out of ten patients had hypohydrosis, 4/10 had angiokeratomas and hearing loss. All male and female patients had abdominal pain and 9/10 had neuropathic pain. Among 7 male patients, 6 had renal complications and 2 of them reached end stage renal disease (ESRD) requiring renal replacement therapy. Concentric left ventricular hypertrophy, was the most common echocardiographic finding along with mitral regurgitation.

Conclusion: ERT may slow down the progression of disease if inititated early. To ensure early diagnosis, it is important to recognize the symptoms of FD. Family screening may help patients to be identified at the presymptomatic phase of the disease.

Key Words: Alpha-galactosidase A, Fabry disease, Multisystemic involvement

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ÖZ

Amaç: Fabry Hastalığı (FH), X'e bağlı geçiş gösteren bir lizozomal depo hastalığı olup, GLA geninde meydana gelen bozukluklara bağlı olarak ortaya çıkmaktadır. Lizozomal alfa-galaktozidaz A (a-Gal-A) enzimindeki etkilenme nedeniyle bazı sfingolipidler çeşitli dokularda birikmekte ve hayati organlarda klinik bulgulara neden olmaktadır. Hastalığa bağlı başlıca klinik bulgular; akroparesteziler, anjiokeratomlar, kornea vertisillata, gastrointestinal, renal, kardiyak ve nörolojik etkilenmedir. Hastalığın tedavisinde enzim replasman tedavisi ve şaperon tedavilerinden faydalanılmaktadır.

Gereç ve Yöntemler: Dr. Sami Ulus Kadın Doğum, Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk Metabolizma Kliniğinde takip edilmekte olan 10 Fabry hastası çalışmaya dahil edildi. Hastalara ait kayıtlar retrospektif olarak, hastane kayıtlarından elde edildi. Hastaların klinik ve genetik özellikleri incelendi. Tam kan sayımı, biyokimya, lyso-Gb3, a-Gal-A düzeyleri, idrar analizi, GLA gen mutasyonları, odyometrik ve oftalmolojik bulgular, ekorkardiyografi ve beyin manyetik rezonans (MR) görüntüleme sonuçları kaydedildi.

Bulgular: 10 Fabry hastasının (7 erkek, 3 kadın) özellikleri incelendi. Hastalarda başta kardiyak, serebrovasküler ve oftalmolojik olmak üzere çok çeşitli klinik bulgular tespit edildi. Çalışmaya dahil edilen tüm olgularda karın ağrısı, 8/10 hastada terleme azlığı, 4/10 olguda anjiokeratomlar ve işitme kaybı, 9/10 nöropatik ağrı mevcuttu. 6/7 erkek olguda hastalığa bağlı renal komplikasyonlar tespit edildi. 2/7 hastada son dönem böbrek yetmezliği nedeniyle diyaliz öyküsü mevcuttu. En sık saptanan ekokardiyografik bulgular sol ventrikül hipertrofisiydi.

Sonuç: Fabry Hastalığının erken tanısı ve enzim replasman tedavisine erken dönemde başlanması prognoz açısından oldukça önemlidir. Aile taraması; semptomlar ortaya çıkmadan olguların tanı almasında yardımcıdır.

Anahtar Sözcükler: Alfa-galaktozidaz A, Fabry hastalığı, Multisistemik tutulum

INTRODUCTION

Fabry disease (FD) is an X-linked lysosomal storage disease (LSD), that occurs due to deficient activity of the enzyme alpha-galactosidase A (a-Gal-A) with multisystemic involvement. The disease can present with a wide range of symptoms, from mild form to the severely affected classical male phenotype with early organ failure and associated morbidity and mortality. The incidence rate varies between 1/476000 and 1/117000. The enzymatic defect leads to accumulation of glycosphingolipids (mainly globotriosylceramide) in various tissues (1).

The classical severe form that presents in hemizygous males during childhood or adolescence with acroparesthesia, anhidrosis, and microalbuminuria. Angiokeratomas, cornea verticillata, and gastrointestinal symptoms may be seen. At a later age, progressive renal failure, hypertrophic cardiomyopathy and cerebrovascular findings may appear. Later onset forms of FD present at adult ages and are generally restricted to one main affected organ (e.g. heart) (2).

Most heterozygous women are also affected, but demonstrate a variable clinical phenotype, due to X-inactivation. Although FD is known to progress more slowly in females and recent studies have shown that heterozygous females are also at significant risk of vital organ dysfunction, including heart and kidneys.

Although awareness of FD has increased in recent years, due to the nonspecific nature of clinical findings, most patients are still diagnosed during late adolescence or adulthood. The average time interval between symptom onset and diagnosis is reported to be 12.5 years for male patients, and 13.1 years for females (3,4).

Diagnosis is made by the confirmation of the enzymatic deficiency through leukocyte analysis. Globotrioacylsphingosine (Gb3), is the substrate of α-Gal A and the main accumulating substance in FD. Plasma Gb3 levels do not correlate with the severity of the disease, and are useful in identifying hemizygous males with the classical phenotype. Lyso-Gb3, is the deacylated derivative of Gb3, has been designated as a hallmark of FD, and is used to identify high risk patients. Due to the fact that heterozygous women may also suffer from the serious effects of FD due to X inactivation, in spite of normal or low-normal enzyme levels, molecular genetic testing is the most reliable method for the diagnosis of females.

Intravenous enzyme replacement therapy (ERT) and oral molecular chaperone therapies are clinically available to patients with FD. ERT which consists of systemic recombinant α-Gal A infusion, was the first approved treatment for FD. There are two available pharmaceutical preparations of recombinant human α-Gal A: agalsidase alfa and agalsidase beta. Both preparations have similar specific activities and enzyme kinetics, and both have been shown to be clinically efficacious. Currently, pegunigalsidase alfa (PRX-102; a covalently cross linked, PEGylated form of α-Gal A), is being evaluated for safety and efficacy in clinical trials. SRT is another option currently under investigation. Gene therapy will likely be a future therapeutic option for patients with FD (5,6).

We conducted a retrospective analysis of 10 patients with FD from three unrelated families.

MATERIALS and METHODS

Ten patients diagnosed with FD at Dr. Sami Ulus Maternity and Child Health Training and Research Hospital were enrolled. Data were collected retrospectively from hospital records. Phenotypic and genotypic presentations of 10 cases from three unrelated families have been evaluated. Diagnoses of relatives of index patients were reached by family screening. Only patients with biochemical and/or genetic diagnosis of FD were

enrolled after collecting an informed consent. Further clinical and laboratory investigations were carried out in all cases as well as documenting the genotypic and phenotypic features of all patients.

Laboratory investigations including complete blood count, biochemistry, lyso-Gb3, α-galactosidase A levels, urinalysis and the mutations detected in the GLA-gene, findings of audiometric and ophtalmological examinations, echocardiograms and cranial magnetic resonance imagings (MRI) were recorded.

Alpha-galactosidase-A enzyme activity was analyzed in leukocytes extracted from 5 cc whole blood samples. The fluorogenic compound 4- Methylumbelliferyl β- D–galactopyranoside (Sigma-Aldrich, USA) was used as the artificial substrate. The measurements were done by RF-5301PC spectrofluorometer (SchimadzuCorp., Japan).

Sequence analysis of GLA gene (NG_007119.1) was carried out for the promoter region, exons and exon-intron junctions of the GLA gene, using genomic DNA samples. Mutation analysis was done using DNA isolated from EDTA blood samples. Polymerase chain reaction amplification of specific exon by the use of specific primers was carried out. The amplicons were purified and then sequenced in both directions in a DNA Sequencing device.

Descriptive statistics were used to express the results as median and range.

The present protocol was approved by the Institutional Review Board of Ankara City Hospital, Ankara, Turkey (E1/1098/2020-16.09.2020). Informed consent was obtained from each study participant. All procedures performed in this work were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the 1975 Declaration of Helsinki and its later amendments, as revised in 2000.

RESULT

This is a retrospective study including a total number of 10 patients between January and December 2019. Fabry disease was diagnosed in all cases by enzymatic analysis in peripheral blood leukocytes, later confirmed by the identification of GLA gene mutation.

Demographic data of the individuals are outlined in Table I. A total of 10 patients including 7 males, (mean age 31.8, range: 14-59 years) and 3 females, (mean age 44.6, range: 40-51 years) were evaluated. All patients were receiving ERT at the time of the study.

Various multisystem manifestations were observed, including cardiac, neurological, cerebrovascular and ophtalmological involvement. The incidences of the clinical findings of patients are as following: 8/10 patients had hypohydrosis, 4/10 had angiokeratomas and hearing loss. All male and female patients had abdominal pain and 9/10 had neuropathic pain. Among 7 male patients, 6 had renal complications and 2 of them reached end stage renal disease (ESRD) requiring renal replacement therapy. Two out of 7 male patients had a history of myocardial infarction. Six patients had mild to moderate concentric left ventricular hypertrophy, which was the most common echocardiographic finding along with mitral regurgitation. Only 1 patient needed the implantation of a pacemaker.

Female patients had variable phenotypes, 1/3 having hypertension and proteinuria, 1/3 having ophtalmological findings, 2/3 having angiokeratomas and neurological findings. 2 female patients had cranial MRI findings including periventricular gliosis and lacunar infarcts.

Lyso-Gb3 levels ranged from 3.5 to 120 ng/ml. At the time of the evaluation, all patients with FD were on enzyme replacement therapy. Comorbid conditions were familial mediteranian fever, ankylosing spondylitis and celiac disease.

GLA gene analyses showed c.(548-1G>C), c.(241_312dup72) and c.(978G>C) hemizygous mutations within different families evaluated (Table I).

DISCUSSION

FD is an inborn error of metabolism with multisystemic presentation and may be overlooked due to the nonspecific clinical findings. Clinically, there are two major subtypes: the early-onset Type 1 ‘classic’ and ‘late-onset’ Type 2 (7).

Affected males with the classic phenotype have deficient a-Gal-A enzymatic activity, marked microvascular endothelial glycosphingolipid accumulation, and childhood or adolescence onset of clinical manifestations. Amongst the affected organs, kidneys are a major target, and particularly in men, Fabry nephropathy leads to end-stage kidney disease by approximately the fourth to fifth decade of life. The most common clinical aspects of Fabry nephropathy are microalbuminuria, proteinuria and/or elevated serum creatinine, with a progressive decline in the glomerular filtration rate (GFR). Glomerular proteinuria is a hallmark of glomerular filtration barrier derangements, mainly due to the accumulation of the substrates of a-Gal-A as globotriasocylceramide (Gb3) and lysotriasocylsphingosine (lyso-Gb3) in endothelial cells and podocytes.

The marker lysoGb3 is now a more widely accepted biomarker of disease activity in both classical and non-classical phenotypes. It has been demonstrated that the early initiation of high dose ERT reduces Gb3 accumulation in cells, decreases lyso-Gb3 in plasma, and also improves symptoms, quality of life and prognosis, and delays the process of kidney dysfunction (8). In our series, lyso-Gb3 levels of FD patients ranged from 3.5 to 120 ng/ml.

Table I: Clinical, biochemical characteristics and GLA mutations in patients with FD erolled in the study.

Family Number	Patient Number	Sex	Age of diagnosis	Alpha-Gal-A level (RR>1.2µmol/l/h)	Lyso-Gb3 level (RR:0-3.5 ng/ml)	Disease causing variant	Clinical findings
1	1	Male	18	0.19	113.3	c.(548-1G>C)	MVP, LVH Retinal tortuosity Hypohidrosis Celiac disease Abdominal pain
1	2	Female	40	0.9	6	c.(548-1G>C)	LVH Abdominal pain Angiokeratomas Cornea verticillata Hypohidrosis
2	3	Male	20	0.1	95.2	c.(241_312dup72)*	LVH Abdominal pain Proteinuria Hypohidrosis
2	4	Female	51	2.4	3.5	c.(241_312dup72)*	Microenfarcts on cranial MRI Abdominal pain Hypohidrosis Anklosing spondilitis
2	5	Male	14	0.4	86.2	c.(241_312dup72)*	MR Retinaltortuosity Abdominalpain
2	6	Female	43	2.1	4.6	c.(241_312dup72)*	MR Abdominal pain Periventricular gliosis on MRI
2	7	Male	44	0.3	99.1	c.(241_312dup72)*	LVH, MR ESRD MI Angiokeratomas FMF Abdominal pain Hypohidrosis
2	8	Male	59	0.4	101	c.(241_312dup72)*	LVH, MR, MI ESRD, FMF Cornea verticillata Angiokeratomas Hypohidrosis Left cereballar infarct, Abdominal pa
2	9	Male	48	0.1	106.5	c.(241_312dup72)*	LVH Proteinuria Abdominal pain Hypohidrosis
3	10	Male	15	0.2	120	c. (978 G>C)	MVP, MR Proteinuria Cornea verticillata Abdominal pain

Previously unreported, novel mutations.* ***MVP:* *mitral valve prolapsus,* ***MR:*** *mitral regurgitation,* ***LVH:*** *Left ventricular hypertrophy,* ***ESRD:*** *end stage renal disease, MI: myocardial infarction,* ***FMF:*** *familial meditteranian fever,* ***a-Gal-A:*** *alpha-galactosidase A*

Two of our male patients had ESRD and 6/7 of male patients had variable degree of proteinuria.

Left ventricular (LV) hypertrophy is the hallmark of cardiac involvement in FD and represents one of the most important causes of morbidity and mortality in affected patients. Coronary microvascular dysfunction has a key role in FD cardiomyopathy, accounting for the considerable prevalence of angina and may also represent the first sign of the disease in patients

with no other sign of cardiac involvement. Linhart et al had shown that about 3 % of patients in his series had left ventricular

hypertrophy (9). In our study, the frequency of left ventricular hypertrophy was 6/10 in addition to mitral valvular insufficiency.

In childhood, patients develop acroparesthesia, which consists of neuropathic pain in their distal extremities. Diffuse pain attacks and crises can also occur, lasting from minutes to days and are often precipitated by rising body temperature due to exercise, fever, or warm environments. Compounding this problem, patients frequently have sweating abnormalities, with the most frequent being anhidrosis or hypohydrosis (10). In our series, angiokeratoma was encountered in a total of 4 patients out of 10. 8/10 patients had hypohydrosis which was the most frequent complaint in our series.

Ophthalmologic opacities, such as cornea verticillata and cataracts, are detected in childhood, but many patients retain intact vision. Concerning the ophthalmologic involvement, cornea verticillata was the most frequent finding in 3/10 of our patients. Only two patients had tortuosity of the retinal veins. Koca et al. (11) had found cornea verticillata in 65.3 % of the patients.

Involvement of the central nervous system (CNS) in FD patients is mainly due to cerebral vasculopathy affecting both small and large cerebral vessels. Macroangiopathy usually leads to ischemic stroke, while microangiopathy is usually the cause of progressive white matter lesions confirmed by magnetic resonance imaging (MRI) in about 80% of FD patients in both genders. Mehta et al discovered cranial MRI abnormalities in 58% of the patients which mainly consisted of white matter abnormalities, cerebral thrombosis and infarction (12,13). In our series MRI abnormalities consisted of chronic ischemic changes, cerebellar infarcts in 2 out of 10 patients.

Early recognition of the disease may lead to initiation of treatment at the early stages of the disease. Family screening is an important aspect in diagnosis of FD, especially for presymptomatic patients (14).

The ERT is the mainstay of FD treatment. Currently, it is widely accepted that ERT provides benefits in terms of cardiac hypertrophy and renal disease, at least when initiated in the early stage of the disease. However, ERT appears to be not effective once target organs are damaged severely. It also usually triggers the production of anti-alpha galactosidase A antibodies, representing a limitation of the treatment and thus leading to unsatisfactory results. More

recently, the use of migalastat (Galafold, AmicusTherapeutics UK), acting as chaperone protein, has been approved to treat FD in case of mutations causing the misfolding of GLA (amenable mutations), and has been reported to improve or stabilize organ damages and reduce lyso-Gb3 plasma level. Recently, in order to obviate the negative aspects of ERT, novel approaches aimed to increase bioavaibility and to reduce immunological response. Gene therapy and gene editing are possible new approaches focused on development (5,14,15).

We identified one novel variant: a large duplication c.(241_312dup72) in exon 2, a known splicing mutation in hemizygous state c.(548-1G>C) and known missense mutation c.(978 G>C) in GLA gene Unfortunately, but pathogenicity of large duplication c.(241_312dup72) in exon 2 was not confirmed by functional analyses. Based on the typical clinical and biochemical characteristics of the patients, the segregation of the genotype in the pedigree, and the analyses of mutation-analyzing softwares, we think that this variant c.(241_312dup72) was responsible for the clinical phenotype. In addition, according to the current criteria recommended by the American College of Medical Genetics and Genomics, these variants can be classified as pathogenic.

The limitation of the study is the small number of patients with FD in our cohort which is, however, an unavoidable consequence of the rare nature of the disease.

CONCLUSION

FD is a multisystemic LSD leading to progressive accumulation of globotriaosylceramide (Gb3) in tissues and organs including heart, kidney, the eyes, vascular endothelium, the nervous system and the skin if left untreated. FD is treatable with disease-specific treatment (enzyme replacement therapy (ERT) or with chaperone therapy). Therefore, the early diagnosis of FD is crucial for reducing morbidity and mortality. To ensure early diagnosis, it is important to recognize the symptoms of FD. Family screening also helps patients to be identified at the early phase of the disease.

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