ORIGINAL ARTICLE

Özgün Araştırma

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Geliş Tarihi : 05 July 2022
Received
Kabul Tarihi : 19 August 2022
Accepted
E Yayın Tarihi : 01 January 2024
Online published

Bu makalede yapılacak atıf
Cite this article as

Serin EN, Atas U, Cetinkaya R, Sari F. The Frequency of Fabry Disease in Hemodialysis Patients in the Western Mediterranean Region of Turkey
Akd Med J 2024;10(1): 92-99

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DOI: 10.53394/akd.1136791

The Frequency of Fabry Disease in Hemodialysis Patients in the Western Mediterranean Region of Turkey

Türkiye'nin Batı Akdeniz Bölgesindeki Hemodiyaliz Hastalarında Fabry Hastalığı Sıklığı

ABSTRACT

Objective:

The aim of the present study was to identify patients with chronic kidney disease of unknown etiology or of other detected etiology among those who were undergoing hemodialysis in the Western Mediterranean region and to detect the prevalence of Fabry mutation in these patients. In addition, we aimed to screen the family members of the cases with mutations in our study.

Methods:

A total of 664 patients over the age of 18 who received hemodialysis treatment in 11 different hemodialysis centers in the Western Mediterranean region of Turkey were screened. Alpha-galactosidase A enzyme levels were first tested in male patients, and for patients with alpha-galactosidase A levels < 3.3 nmol/mL/h, GLA gene sequence analysis was performed. GLA gene sequence analysis was performed directly in female patients.

Results:

In total 664 patients [313 (47.1%) male and 351 (52.9%) female] have been scanned. Fabry mutation was positive in eight female patients and one male patient.

Conclusion:

According to the output of the research, the prevalence of Fabry disease among the patients who received hemodialysis treatment was determined as 1.35%. In order to eliminate the conflicts upon whether the mutations which is effective on the etiology of Fabry disease are pseudo alleles it is required that new researches should be done, prospective scanning programs in a wider patient population and genetic consultancy and preventive medicine services should become more prevalent.

Key Words:

Fabry disease, Chronic kidney disease, Hemodialysis

ÖZ

Amaç:

Bu çalışmanın amacı, Batı Akdeniz bölgesinde hemodiyaliz uygulanan ancak böbrek yetmezliği etiyolojisi bilinmeyen veya başka nedenlere bağlanan hastaları belirlemek ve bu hastalardaki Fabry mutasyonunun prevalansını saptamaktır. Ayrıca, çalışmamızda mutasyon saptanan olguların aile bireylerinde de tarama yapmayı amaçladık.

Yöntemler:

Türkiye'de Batı Akdeniz bölgesinde 11 farklı hemodiyaliz merkezinde hemodiyaliz tedavisi gören 18 yaş üstü 664 hasta tarandı. Erkek hastalarda ilk olarak Alfa-galaktosidaz A enzim seviyeleri test edildi ve alfa-galaktosidaz A seviyeleri < 3,3 nmol/mL/saat olan hastalarda GLA gen dizi analizi yapıldı. Kadınlarda ise GLA gen dizi analizi doğrudan yapıldı.

Bulgular:

Toplam 664 hasta [313 (%47,1) erkek ve 351 (%52,9) kadın] tarandı. Fabry mutasyonu sekiz kadın hastada ve bir erkek hastada pozitifti.

Sonuç:

Araştırmamızda hemodiyaliz tedavisi alan hastalarda Fabry hastalığı prevalansı %1,35 olarak belirlendi. Fabry hastalığının etiyolojisinde etkili olan mutasyonların yalancı alel olup olmadığı konusundaki çelişkileri ortadan kaldırmak için yeni araştırmaların yapılması, daha geniş hasta popülasyonunda prospektif tarama programlarının yapılması, genetik danışmanlık ve koruyucu hekimlik hizmetlerinin yaygınlaştırılması gerekmektedir.

Anahtar Kelimeler:

Fabry hastalığı, Kronik böbrek hastalığı, Hemodiyaliz

INTRODUCTION

Fabry disease is an X-linked recessive inherited disorder of glycosphingolipid metabolism and a lysosomal storage disease. The absence or decreased activity of the alpha-galactosidase A enzyme encoded by the galactosidase alpha (GLA) gene on chromosome band Xq22 leads to inadequate lipid metabolism and progressive lysosomal accumulation of globotriaosylceramide (Gb3) that has terminal alpha-galactosyl residues (1,2).

The worldwide prevalence of Fabry disease is estimated to be one in 117.000 live births and one in 40.000 men (3,4). Fabry disease, which is associated with a wide variety of symptoms and multisystemic involvement in the clinical presentation, including acroparesthesia, gastrointestinal symptoms, angiokeratoma, cornea verticillata, cerebrovascular disease, and hypertrophic cardiomyopathy, is also one of the rare causes of chronic kidney disease (CKD) (1,5,6). There are classic and severe forms of the disease as well as its cardiac and renal variants (7-9). Due to its variants and random X inactivation in women, it is observed with different phenotypic presentations, at different ages and with various systemic effects. In cases of renal involvement, it leads to fibrosis, glomerulosclerosis, and progressive renal insufficiency due to the accumulation of Gb3 in podocytes, mesangium, glomerular endothelium, distal tubular epithelium, arterial and arteriolar endothelial and smooth muscle cells, and interstitial cells (10,11).

Currently, among the existing CKD patients worldwide, there is a group of patients with unknown etiology. In patients from Turkey for whom first renal replacement therapy (hemodialysis) was started in 2018, a group comprising 15.1% patients with CKD of unknown etiology was detected (12). It is estimated that Fabry patients who have not yet been diagnosed are also included in this group with unknown etiology. Studies have been conducted around the world to screen high-risk populations [patients undergoing dialysis, patients who had a stroke at an early age (18-40 years), patients with ventricular hypertrophy without a cause etc.] for detecting undiagnosed Fabry patients (11,13,14). Increased screening and diagnostic programs facilitate the diagnosis of Fabry disease at an early stage before the development of clinical symptoms or in suspected cases.

The detection of alpha-galactosidase A levels and lyso-Gb3 (globotriaosylsphingosine) as well as genetic testing can be used for the screening and diagnosis of Fabry disease (15,16). Testing for alpha-galactosidase A in the blood is quite sensitive and specific for men, whereas it can give false-negative results in women (17). The deoxyribonucleic acid (DNA)-based genetic test for detecting the sequence of GLA gene exons is the most important diagnostic test for Fabry disease (18). At present, a multisystemic approach, supportive treatment, enzyme replacement therapy (ERT), and/or chaperone therapy (migalastat) are used to treat the disease (19,20). It is important to diagnose the disease as early as possible and to start ERT for preventing multiorgan dysfunction without lysosomal Gb3 accumulation (18). The aim of the present study was to identify patients with CKD of unknown etiology or of other detected etiology among those who were undergoing hemodialysis in the Western Mediterranean region but had underlying Fabry disease and to detect the prevalence of Fabry mutation. In addition, we aimed to perform first-degree family screening of index cases and clinical screening in positive cases. Moreover, we aimed to draw attention to the fact that a rare storage disease such as Fabry disease may be the underlying etiology in these patients.

MATERIAL and METHODS

In the present study, 664 patients aged above 18 years who were undergoing hemodialysis at 11 different hemodialysis centers in the Western Mediterranean region were screened for Fabry disease after obtaining approval from the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Protocol no: 397, 29th of June, 2016) and in accordance with the decisions of the Helsinki Declaration. The study was conducted in accordance with research and publication ethics, by obtaining written informed consent from the patients.

Alpha-galactosidase A enzyme levels were first tested using enzyme-linked immunosorbent assay method in male patients, and for patients with alpha-galactosidase A levels < 3.3 nmol/mL/h, GLA gene sequence analysis using “Sanger method” was performed. GLA gene sequence analysis was performed directly using the Sanger method in female patients. First-degree relatives of patients testing positive for GLA gene mutations

were also included in genetic screening. All patients diagnosed with Fabry disease underwent electrocardiogram (ECG) and echocardiography (ECHO) screenings as well as neurological, dermatological, and eye examinations.

A written consent was obtained from all patients who underwent the screenings. Data on age, gender, additional disease, dialysis duration, and CKD etiology were obtained from patients, dialysis centers databases, and Medulla Physician system database. Death-related information on patients who died was obtained from the Turkish Public Health Institution Notification System.

Descriptive statistics were used from the obtained data using SPSS 18.0 package program and were presented as frequency, percentage, mean, and standard deviation values.

RESULTS

In the present study, 664 patients [313 (47.1%) male and 351 (52.9%) female; age range, 20–96 years] from 11 different hemodialysis centers were included. The etiology of CKD was unknown in 122 (18.4%) of the 664 patients. The causes of CKD in patients with known etiology are listed in Table I.

Table I: Diseases detected in chronic kidney disease etiology in patients participating in the study.

	Number of positive patients (n)	Percentage (%)
Diabetes Mellitus	157	23.6
Hypertension	298	44.9
Glomerulonephritis	80	12
Polycystic Kidney Disease	17	2.6
Tubulointerstitial Nephritis and Obstructive Nephropathies	81	12.1
Amyloidosis	12	1.8
Connective Tissue Disease - Vasculitis	15	2.2
Nephrolithiasis	14	2.1
Unknown Etiology	122	18.4
Other	32	4.8

Other: Gout, Hepatitis B and Hepatitis C, Sickle cell anemia, Renal cell cancer, Human acquired immunodeficiency virus infection, Atypical hemolytic uremic syndrome, Malignancy.

Alpha-galactosidase A enzyme levels were tested in all male patients participating in the study; the levels were normal in 256 (81.8%) and low in 57 (18.2%) patients (Alpha-galactosidase A < 3.3 nmol/mL/h). Of the 57 male patients, seven could not be reached for performing gene analysis. Fabry mutation was positive in one of the 50 men in whom GLA gene analysis was performed. GLA gene analysis was performed in all women who participated in the study. Fabry mutation was negative in 343 (97.8%) and positive in eight (2.2%) female patients. Thus, in the present study, there were nine patients (eight female, one male) with positive GLA gene mutation and Fabry mutation prevalence was 1.35% (Figure 1).

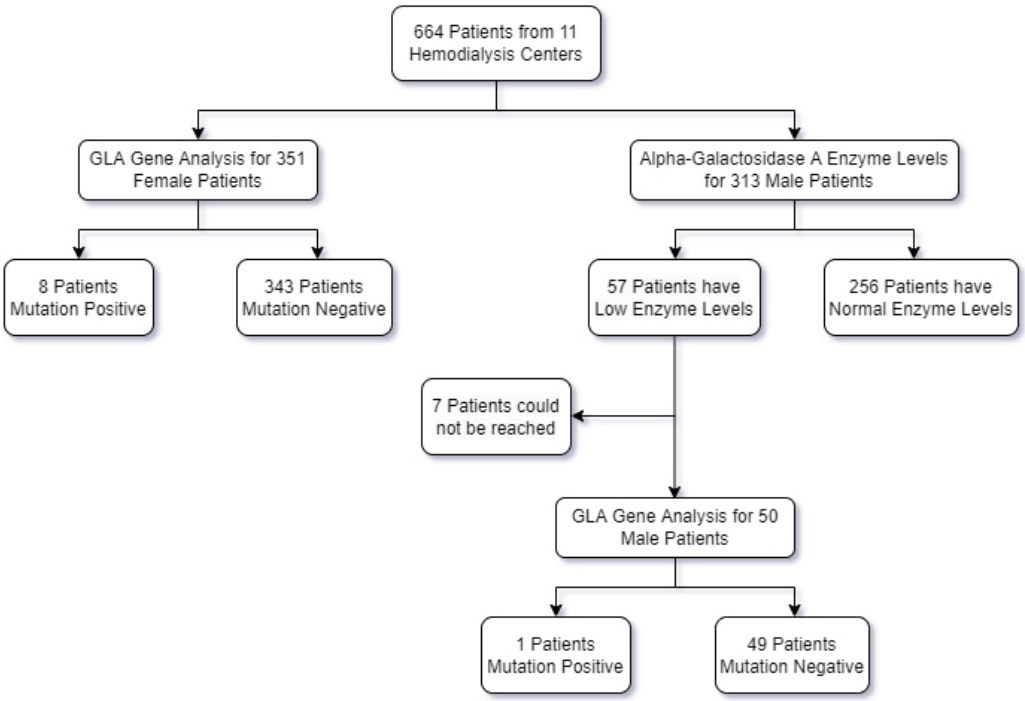

Figure 1: Distribution of patients according to enzyme level and mutation.

The male patient testing positive in the genetic analysis had a D313Y mutation; six of the positive female patients had a D313Y mutation, one had an S126G mutation, and the remaining one had an R363C mutation.
Five of the nine patients testing positive for genetic mutation refused to undergo further examinations and treatment, and their families refused to be screened. Relatives of one patient who died during the study period also refused to undergo genetic screening. The remaining three female patients who had tested positive for a mutation agreed to undergo further examinations and treatment, and their relatives agreed to undergo family screening; thus, their screening was performed.

Index case-1

In the first of the three female patients who underwent further examinations, D313Y mutation was positive. The medical history of the patient showed that she had diabetes mellitus and hypertension and had experienced myocardial infarction; furthermore, she had a history of vision loss and inferior vena cava thrombosis. T-wave negativity and minimal ST depression were detected on ECG, and concentric hypertrophy in the left ventricle was observed on ECHO. Electromyography (EMG) revealed mixed sensorimotor polyneuropathy. Her first-degree relatives were examined for Fabry disease, but no positive cases were detected.

Index case-2

In the second female patient, R363C mutation was positive. The medical history of the patient showed that she had diabetes mellitus and hypertension; furthermore, she had experienced myocardial infarction and had undergone bypass surgery. Her ECG revealed T-wave negativity, ST depression, and QRS enlargement and ECHO revealed left ventricular hypertrophy and hypokinesis in the inferior wall. Eye examination revealed bilateral optic atrophy and dot hemorrhage in the right eye macula. Mixed sensorimotor polyneuropathy was detected on EMG. Four persons among the first-degree relatives of the patient were screened, and in one son, the enzyme activity was below normal and lysosomal accumulation of lyso-Gb3 was high: 10.9 ng/mL (0–3.5 ng/mL). The GLA gene mutation detected in this son was the same as that in the mother, i.e., R363C mutation was present. His medical history showed that he had hypertension and asthma. Eye examination revealed lipid accumulation in the fovea in the inferotemporal and superior peripheral regions. Signs of hypertrophy were detected on ECG. Left ventricular hypertrophy was detected on ECHO. ERT was initiated for the patient before the clinical symptoms of Fabry disease developed.

Index case-3

In the third patient, D313Y mutation was positive. The patient's medical history showed that she had hypertension. ECG revealed signs of hypertrophy; ECHO showed left ventricular septal hypertrophy and relaxation defect. The patient's EMG report could not be accessed, but her neurological examination revealed that she had pain and paresthesia. Seven first-degree relatives of the patient were genetically analyzed, and D313Y mutation was positive in one son and four daughters. The relatives of the patient in whom the mutation was detected refused to undergo further examination.
In summary, all of these three patients who were screened for other pathologies that may be associated with Fabry disease, had acroparasthesia, two had myocardial infarction, and one had cataract.

DISCUSSION

In the present study, a total of 664 patients, including 351 female and 313 male patients, undergoing hemodialysis at 11 different centers were screened. The GLA gene mutation was positive in nine patients (eight female and one male), including D313Y in seven, S126G in one, and R363C in one patient.
Fabry disease is a public health problem, and awareness levels regarding this disease are low (21). It is often overlooked in clinical practice due to its multisystemic and non-specific effects and different variants.
In the present study, 664 patients undergoing hemodialysis in the Western Mediterranean region were screened, and the prevalence of Fabry mutation was calculated to be 1.35% (9/664). In two similar studies conducted in Turkey, screening of 1136 patients revealed a prevalence of 0.17% and screening of 1527 patients revealed a prevalence of 0.3% (22,23). Compared with the results of these studies, the prevalence in the present study was higher. In two studies conducted on 5657 patients with renal transplant and 313 non-dialysis patients with end-stage renal disease who were at high risk for Fabry disease, the prevalence rates were found to be 0.67 and 0.95, respectively (24,25). Many studies have been conducted worldwide to determine the renal effects of Fabry disease. The prevalence of Fabry disease in patients undergoing dialysis was 0.02% in Japan, 0.24% in Italy, 0.12% in northern Brazil, and 0.36% in Russia (11,26-28). The results of the present study conducted in Turkey and those conducted worldwide are affected by regional differences in the studies and different interpretations of the detected genetic mutations.

The prevalence of Fabry mutation determined in the present study is higher than those reported in other studies. This is attributable to the number of patients screened in the present study being lower than those in other studies, regional factors such as high rate of marriages between relatives, and the assumptions of positive D313Y and S126G mutations. Consanguineous marriages and different genetic diseases such as Fabry disease are more common in closed societies such as the Middle East and Turkey (29-31). Some studies have reported that D313Y is a pseudoallel and that S126G is an ambiguous genetic variant (32-36). If we assume D313Y and S126G mutations as negative, the prevalence in the present study would be similar to those reported in studies from other countries (0.15%).
D313Y mutation was detected in seven (six female patients), R363C mutation in one, and S126G mutation in one of our index patients. D313Y mutation has previously been found in asymptomatic individuals, leading to a suspicion in terms of its clinical manifestation. A subsequent study has reported that D313Y mutation leads to organ findings and elevated lyso-Gb3 biomarker levels and that it plays a role in the appearance of

neurological symptoms and findings, such as pain and cerebrovascular accidents, and eye findings, but ERT should be administered in symptomatic patients with a D313Y mutation (37). However, some studies have reported that D313Y mutation leads to a lack of pseudo-alpha-galactosidase A activity (32-35,38). This issue has not been clarified yet.

While four of our GLA gene mutation-positive patients previously had CKD of unknown etiology, CKD was associated with different causes in five patients. This indicates that Fabry disease should be considered in some patients with CKD of known etiology as well as those with CKD of unknown etiology. In the present study, the number of female patients testing positive for mutation was higher than the number of such male patients. In some studies, only enzyme analysis was performed for female patients, but we directly analyzed GLA gene mutation due to false negativity concern (39,40). This may have made it easier for us to identify positive female patients. In addition, women were overlooked for Fabry screening in studies around the world considering that they were only carriers due to X-linked inheritance (28,41,42). However, studies have shown that the disease may clinically manifest itself in women as well due to random X inactivation (10). Eight of our index patients were female, and R363C mutation, which causes the classical Fabry phenotype, was found in one of them (43). In addition, the same mutation was detected and ERT was initiated in this patient's 40-year-old son, who was asymptomatic. This suggests that considering women to be the carriers of Fabry disease and not performing examinations for them can lead to overlooking of many patients.

CONCLUSION

An individualized patient approach is recommended because of the clinical heterogeneity of Fabry disease. Awareness of all clinicians, especially nephrologists, should be increased regarding Fabry disease, which may be easily overlooked, because it is rare, can be asymptomatic up to a certain age, and has variants. Evaluation of patients at risk for Fabry disease, primarily those who develop renal insufficiency of unknown etiology at an early age, may prevent potentially increased renal dysfunction as well as other tissue and organ damage that may eventually occur. Additionally, it is important to perform family screening of an index patient in whom the disease is detected so that diagnosis can be made and early treatment can be started in patients who are still asymptomatic.

Acknowledgements:

The authors would like to thank all patients who participated in this study. The authors would also like to thank all hemodialysis centers that participated in this study and INTERGEN (Genetics and Rare Diseases Diagnosis Research and Application Center).

Ethics Committee Approval:

The study was carried out after obtaining approval from the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Protocol no: 397, 29 June 2016), in line with the Helsinki Declaration decisions.

Informed Consent:

All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Author contributions:

E.N. S., and R. C. developed the study concept. All authors performed the study and wrote the manuscript. All authors assessed the results and critically reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of Interest:

The authors declare that there is no conflict of interest.

Financial Disclosure:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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