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The Frequency of Fabry Disease in Acute Stroke Patients with Renal Insufficiency in Sakarya Province

Sakarya İli Akut İskemik İnme ve Kronik Renal Yetmezlikli Olgularda Fabry Hastalığı Sıklığı

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ABSTRACT

Aim: This study aimed to investigate the frequency, clinical and genetic characteristics, and therapeutic options associated with Fabry disease (FD) in individuals with acute stroke and concomitant renal insufficiency.
Material and Methods: An FD screening was performed on adult patients with renal dysfunction who were admitted to the neurology clinic due to acute stroke between 2015 and 2021. Screening was performed by a leukocyte α-galactosidase A (α-Gal A) enzyme activity assay using dried blood spot (DBS) samples from male patients. In cases where the enzyme activity was less than 2.5 nmol/ml/h, genetic analysis was performed. Female patients underwent direct genetic analysis.
Results: Renal dysfunction was detected in 39 ischemic stroke patients and 5 hemorrhagic stroke patients out of a total of 401 cases. The enzyme level was found low in only one of the male patients. The c.680G>A (p.R227Q) mutation was observed in this male patient and a female patient. In the later stages of the study, it was realized with the help of pedigree analysis that these two cases were first-degree relatives. The same mutation was also detected in 13 first-degree and 2 second-degree relatives. The frequency of FD in our study group, which included patients with cerebral and renal involvement regardless of consanguinity, was 4.54%.
Conclusion: Rapid detection of FD cases can be achieved by screening individuals presenting with multiple end-organ damages. To the best of our knowledge, this study highlights the underemphasized association between renal involvement and stroke in FD.
Keywords: Fabry disease; renal insufficiency; cerebrovascular disease.

ÖZ

Amaç: Bu çalışmada, böbrek yetmezliği olan akut inme hastalarında Fabry Hastalığı (FH) sıklığı ile klinik ve genetik özelliklerinin ve tedavi seçeneklerinin araştırılması amaçlandı.
Gereç ve Yöntemler: 2015 ve 2021 yılları arasında nöroloji kiniğine akut inme nedeniyle yatırılan ve böbrek fonksiyon bozukluğu tespit edilen erişkin hastalarda FH taraması yapıldı. Tarama, erkek hastalardan alınan bir kuru kan lekesi (dried blood spot, DBS) örnekleri ile lökosit α-galactosidase A (α-Gal A) enzimatik aktivite değerlendirmesine ile yapıldı. Enzim aktivitesi 2,5 nmol/ml/saat'in altında tespit edilen vakalarda genetik inceleme yapıldı. Kadın hastalarda ise doğrudan genetik analiz uygulandı.
Bulgular: Toplam 401 olgudan 39 iskemik inme olgusunda ve 5 hemorajik inme olgusunda renal disfonksiyon saptandı. Erkek hastalardan sadece birinde enzim düzeyi düşük bulundu. Bu erkek hastada ve bir de kadın hastada c.680G>A (p.R227Q) mutasyonu tespit edildi. Çalışmanın ilerleyen aşamalarında pedigri analizi ile bu iki olgunun birinci derece akraba olduğu fark edildi. Aynı mutasyon 13 birinci derece ve 2 ikinci derece akrabada da tespit edildi. Akraba evliliğinden bağımsız olarak hem beyin hem de böbrek tutulumu olan hastaları içeren çalışma grubumuzda FD sıklığı %4,54 idi.
Sonuç: Çoklu uç organ hasarı olan bireylerin taranması ile FH olgularının erken tespitinde başarı sağlanabilir. Bildiğimiz kadarıyla bu çalışma, FH'da böbrek tutulumu ve inme arasında kapsamlı bir şekilde vurgulanmamış olan bu ilişkiyi vurgulamaktadır.
Anahtar kelimeler: Fabry hastalığı; böbrek yetmezliği; serebrovasküler hastalık.

INTRODUCTION

Fabry disease (FD) is a rare X-linked progressive lysosomal storage disorder known for its multisystem manifestations, including neuronal and vascular complications. Its prevalence ranges from 1/3100 to 1/117,000 in European adults and has been reported to be as high as 1/1250 in newborns (1,2). If left untreated, the life expectancy for FD patients is approximately 60 years for males and 75 years for females (3).

FD is the result of mutations in the GLA gene located on the X chromosome (4). In patients with FD, dysfunction of the α-galactosidase A (α-Gal A) enzyme leads to the gradual accumulation of globotriaosylceramide (Gb3) and its by-products in various cellular compartments, particularly lysosomes (5).

Typical clinical manifestations of FD include early symptoms such as angiokeratomas, acroparesthesias, sweating irregularities, and gastrointestinal problems that typically begin in childhood or adolescence. Late-onset symptoms, which appear between the third and fifth decades of life, include vasculopathy, cerebrovascular disease, cardiomyopathy, and renal failure (6,7). In males, the diagnosis of FD is based primarily on the identification of reduced leukocyte α-Gal A enzyme activity, usually by dried blood spot (DBS) testing, followed by GLA gene analysis to identify the specific mutation. However, genetic analysis is recommended as the initial diagnostic approach for females (8).

Management of FD includes enzyme replacement therapy (ERT) and/or chaperone therapy (9). A multidisciplinary approach is required for the management of adult FD. In addition, individual disease phenotypes and organ involvement should be taken into account before starting ERT. ERT should not be delayed after diagnosis, as even asymptomatic cases require comprehensive follow-up and the administration of supportive treatments for FD-related symptoms (10). Nevertheless, renal failure, stroke, and sudden cardiac death are the most common causes of mortality in FD (11). Among adults with FD, stroke and renal dysfunction are the most common major organ impairments. To the best of our knowledge, no previous studies have investigated the prevalence of FD in patients with acute cerebrovascular stroke and concurrent renal dysfunction. Therefore, this study aimed to investigate the prevalence and clinical and genetic characteristics of FD patients with acute stroke and concomitant renal dysfunction.

MATERIAL AND METHODS

In this retrospective study, we enrolled patients who were admitted to the Neurology Department of Sakarya University Training and Research Hospital and diagnosed with acute ischemic or hemorrhagic stroke with concomitant renal dysfunction between January 2015 and November 2021.

Written informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of Sakarya University (January 03, 2022, and 558).

Inclusion criteria included individuals aged 18 to 80 years with acute stroke and renal dysfunction. Renal dysfunction was defined as the presence of microalbuminuria, previously diagnosed chronic renal failure, or participation in a regular dialysis program. We carefully collected demographic information and clinical characteristics, performed physical examinations, obtained laboratory test results, and documented radiologic and echocardiographic findings. Of particular importance during the physical examination were assessments for angiokeratoma and concentric ventricular hypertrophy, as these are commonly associated with FD.

In male patients, FD screening included the use of a DBS assay to measure leukocyte α-Gal-A enzymatic activity. Genetic analysis targeting the GLA gene was performed in males whose enzyme activity was <2.5 nmol/ml/hour. In contrast, female patients underwent direct genetic analysis. Screening for GLA gene mutations was performed by Sanger sequence analysis using polymerase chain reaction amplification followed by Sanger DNA sequencing (ARCHIMED Laboratory, Vienna, Austria). The GLA gene is located on Xq22 and spans 13 kb of genomic DNA (7 exons and a cDNA sequence of 1290 bases). Exons 1-7 of the GLA gene coding sequences, together with adjacent intronic sequences (minimum 20 base pairs), were amplified from pure genomic DNA and sequenced in both forward and reverse directions. Targeted mutation analysis of a single exon was possible. Patient sequences were compared with reference DNA sequences for comprehensive analysis.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS version 23.0. The descriptive statistics were calculated. The continuous variables were presented as mean±standard deviation, the categorical variables were as numbers or percentages. Student t-test was used to compare numerical data between groups, and the chi-square test was used to compare categorical data. All statistical tests reported were two-tailed, with the significance level at <0.05.

RESULTS

A total of 401 patients with acute stroke and renal dysfunction, who were hospitalized between January 2015 and November 2021, were initially considered for inclusion in this study. Forty-four patients who met the inclusion criteria were included in this study of this cohort of patients with acute stroke and concurrent renal dysfunction, 39 (88.6%) had ischemic stroke and the remaining five (11.4%) had hemorrhagic stroke. Both groups had a similar gender distribution and age profile (p=0.411, and p=0.361, respectively). Within this cohort, 42 (95.5%) patients had chronic renal insufficiency, eight of whom were on regular dialysis. The remaining two (4.5%) patients had proteinuria during their hospitalization.

The stroke type, demographic characteristics, and chronic diseases of the patients in the study were presented in Table 1. Two patients included in the study were diagnosed with FD. Notably, they were first-degree relatives. Their clinical, laboratory, radiologic, and genetic characteristics were presented in Table 2.

The enzymatic activity of α-Gal A enzyme was found to be <2.5 nmol/mL/hr (0.1 nmol/h/mL; normal >1.2) in the male patient with ischemic stroke, subsequent genetic analysis revealed the presence of the c.680G>A (p.R227Q) missense mutation. With these results, the patient was

Table 1. The characteristics of the patients with ischemic stroke and hemorrhagic stroke

	Ischemic Stroke (n=39)		Hemorrhagic Stroke (n=5)	
	Male (n=22)	**Female (n=17)**	**Male (n=2)**	**Female (n=3)**
Age (years)	60.5±14.6	62.3±16.5	59.0±2.8	75.3±23.5
Chronic Disease, n (%)				
Hypertension	14 (63.6)	11 (64.7)	2 (100)	2 (66.7)
Diabetes mellitus	9 (40.9)	7 (41.2)	0 (0.0)	2 (66.7)
Coroner artery disease	4 (18.2)	5 (29.4)	0 (0.0)	1 (33.3)
Cerebrovascular disease	2 (9.1)	6 (35.3)	0 (0.0)	1 (33.3)
Congestive heart failure	1 (4.5)	1 (5.9)	0 (0.0)	0 (0.0)
Cirrhosis	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)
Atrial fibrillation	1 (4.5)	2 (11.8)	0 (0.0)	0 (0.0)

Table 2. The clinical, laboratory, radiologic, and genetic features of patients with Fabry disease

	Index Case	**Other Case**
Age	43 years	45 years
Symptom	Left 4+/5 hemiparesia, left hemihypoestesia	Hypoestesia on the right arm, right homonymous hemianopsia
ECG	Normal sinus rhythm	Normal sinus rhythm
Radiological Findings		
Brain CT	Isodense	Isodense
Brain MRI	a left side pontine ischemic lesion	left occipital lobe ischemic lesion
CDUS	bilateral non-stenotic atherosclerotic plaque	right vertebral artery flow 60 ml/min, left vertebral artery flow 70 ml/min, means vertebro-basillar insufficiency
Echo	60% ejection fraction, mild mitral regurgitation, atrial insufficiency, and left ventricular hypertrophic concentric cardiomyopathy (HCM)	60% ejection fraction and normally left systolic function
Laboratory Findings (nv)*		
Urea (17-43)	115 mg/dL	14 mg/dL
Cr (0.67-1.17)	10.24 mg/dL	0.58 mg/dL
UA (3.5-7.2)	5.6 mg/dL	3.9 mg/dL
LDL (<130)	123 mg/dL	143 mg/dL
HDL (>40)	31 mg/dL	51 mg/dL
VLDL	69.2 mg/dL	23.2 mg/dL
TG (0-200)	346 mg/dL	116 mg/dL
TC (0-200)	174 mg/dL	205 mg/dL
Proteinuria	1+	2+
Physical examination		
Angiokeratoma	none	none
Corneal symptoms	none	none
α-Gal A activity	0.1 nmols/h/mL	-
GLA gene analysis	c.680G>A (p.R227Q) missense mutation	c.680G>A (p.R227Q) heterozygote missense mutation

ECG: electrocardiography, CT: computed tomography, MRI: magnetic resonance imaging, CDUS: carotid vertebral Doppler ultrasonography, Echo: echocardiography, (nv)*: normal reference values of laboratory parameters were shown in brackets, Cr: creatinine, UA: uric acid, LDL: low-density lipoprotein, HDL: high-density lipoprotein, VLDL: very-low-density lipoprotein, TG: triglyceride, TC: total cholesterol, α-Gal A: α-galactosidase A

diagnosed with FD and defined as an index case (ZS). This patient had a history of recurrent fevers, neuropathic symptoms in the distal extremities, acroparesthesias, intolerance to temperature extremes, hypohidrosis, and gastrointestinal disturbances since childhood. There were no angiokeratomas or corneal symptoms. The patient received peritoneal dialysis. He was subsequently referred to our nephrology clinic for further evaluation. ERT was initiated with intravenous α-galactosidase beta (1.0 mg/kg) administered biweekly. However, his renal insufficiency progressed to end-stage renal failure, necessitating a switch from peritoneal dialysis to hemodialysis after one year. He then underwent hemodialysis three times a week for two years, after which he sought a kidney transplant from his spouse. Currently, he is 49 years old, has been on ERT for six years, and no longer requires dialysis. Importantly, he has had no recurrence of stroke.

The second patient, the sister of the index case (FT), was hospitalized with an ischemic stroke. She was found to have the same mutation as her sibling. At the time of diagnosis, she had only microproteinuria as a renal sign. ERT was initiated for her with intravenous α-galactosidase beta (1.0 mg/kg) administered biweekly. She was subsequently referred to our nephrology clinic for comprehensive follow-up.

FD is a genetically inherited disease so family screening was performed on the index case to detect asymptomatic cases. With the scope of the family screening, genetic analysis was performed on the siblings and offspring of our index case (ZS). But, we could not perform genetic analysis on the mother and father. The same genetic mutation was identified in a total of 9 females who shared first-degree consanguinity with the index case (including 6 sisters and 3 daughters), 4 males (his brothers), and 2 males who were his nephews, representing second-degree consanguinity (Figure 1). The whole family member's preference for cousin marriage caught our attention. We think that the reason why the X-linked recessive disease shows an autosomal dominant transmission pattern is due to consanguineous marriage preferences within the family. Notably, the sisters of the index case remained asymptomatic at the time of their FD diagnosis. However, one of them (FT) experienced an ischemic stroke in the second year after confirmation of FD and initiation of prophylactic ERT. The brothers of the index case were all asymptomatic at the time of diagnosis. Unfortunately, one of them succumbed to intraparenchymal hemorrhage during the second year of ERT at the age of 35. Among the 20 relatives, one nephew with a history of cryptogenic

stroke at a young age and proteinuria was identified as having FD. In addition, three children of the index case were diagnosed with FD during the asymptomatic phase and subsequently started prophylactic ERT.

In this study, two cases from the same family were included. We performed frequency analysis only on the male FD patients within the study group due to the consanguinity between the cases. The prevalence of FD in Sakarya province was calculated to be 4.54% within the cohort of patients characterized by dual end-organ damage involving both the kidneys and the brain. However, when individuals from the same lineage were included, the observed frequency increased to 8.8% (including patients with stroke and kidney injury as independent criteria). As a result, this approach allowed us to identify and evaluate a more concentrated group of patients.

DISCUSSION

Fabry disease is a rare metabolic disorder characterized by extensive organ involvement resulting from vascular damage. This involvement can lead to severe dysfunction of the nervous, renal, and cardiac systems, with potentially fatal consequences. Given its X-linked inheritance pattern, recent research has revealed differences in gene expression on the X chromosome between male and female ischemic stroke patients (12). The clinical manifestations of FD can vary significantly in heterozygous female patients due to X chromosome inactivation (13). The pedigree of our cases shows an autosomal dominant transmission pattern. We think that the preference of all family members for cousin marriage is effective in the OD transmission pattern in the x-linked recessive disease. Within the spectrum of FD, those with α-Gal A enzyme activity below 1% are classified as having the classical form, whereas those with enzyme activity between 1% and 30% are classified as having the atypical form (14). Classical FD typically presents with multiorgan involvement, while atypical FD often presents with single-organ involvement (7).

The hallmark symptoms of FD, such as angiokeratomas, corneal ectropion, and heat- and exercise-induced neuropathic pain (acroparesthesia), may become apparent in childhood (7). In contrast, adult FD complications, including proteinuria, chronic kidney disease, cryptogenic concentric left ventricular hypertrophy (LVH), young cryptogenic stroke, cerebral white matter lesions, and occlusive cerebrovascular events, tend to develop progressively over the following years (6).

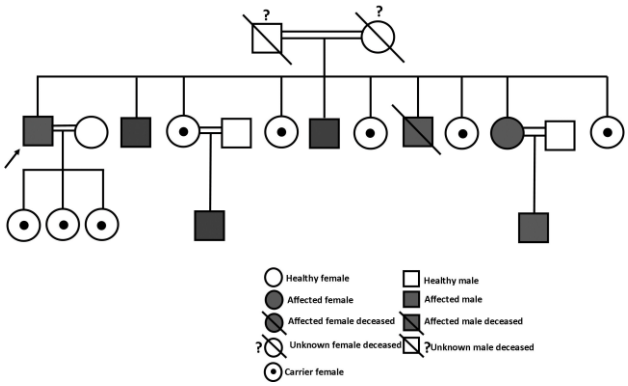

Figure 1. The pedigree of index case

Ischemic stroke is the most common type of cerebrovascular event in individuals with FD. The reported incidence of FD in the context of stroke varies in the literature. The estimates suggest that it accounts for approximately 1% of young stroke cases, 0.35% in ischemic stroke or transient ischemic attack (TIA), and 0.2% in unselected stroke populations. In our study, two patients were diagnosed with FD after ischemic stroke (15-17). No FD was found in patients with hemorrhagic stroke.

Notably, cerebrovascular events in FD patients are particularly common in individuals aged 25 to 44 years, in contrast to the general population (10,13). Our study is consistent with this pattern, as the patients diagnosed with FD after stroke were aged 43 and 45 years. Furthermore, our analysis showed that the incidence of stroke was significantly higher in individuals with FD than in the general population across all age groups (18).

Renal dysfunction is a significant complication of FD following cerebrovascular events. One of the most common symptoms is proteinuria, which typically manifests in the second or third decade of life. As individuals with FD age, the pathological accumulation of glycosphingolipid deposits progressively intensifies, leading to a gradual decline in renal function, a reduction in glomerular filtration rate (GFR), and eventually the need for dialysis or kidney transplantation (6). The prevalence of FD in hemodialysis patients is estimated to be 0.15% to 1.2%, and it is approximately 2% in individuals with chronic kidney disease who do not require dialysis (19,20). In our study, the male patient was undergoing peritoneal dialysis at the time of his FD diagnosis, whereas the female patient had only microproteinuria at the time of her FD diagnosis. Both patients were started on ERT. The American Heart Association/American Stroke Association guidelines for 2021 recommend α-galactosidase ERT for patients with ischemic stroke in FD, assigning it a Class 2 recommendation with a Level B-NR rating (21). ERT has demonstrated efficacy in alleviating neuropathic pain, improving GFR, and reducing QRS complex duration (22). In addition, ERT is recognized for its ability to attenuate vasculopathic lesions in the brain (23). However, the extent to which ERT can reduce the incidence of stroke remains controversial (22,24).

Nervous system disorders and renal dysfunction are life-threatening complications of FD. When both systems are affected simultaneously, they contribute to a more severe clinical phenotype. The pathophysiological mechanisms underlying renal and nervous system dysfunction in FD show similarities. Emerging evidence suggests that inadequate renal function may be associated with the presence of chronic white matter hyperintensities, highlighting a potential link between the two (23).

The coexistence of cerebrovascular and renal disease is an emerging area of investigation in the context of FD. There are studies in the literature showing the long-term effects of renal dysfunction in young stroke patients (25). Existing literature provides limited insight into the prevalence of FD associated with chronic renal failure and stroke in general. In a study by Rolfs et al. (26), FD was identified in 13 of 39 patients with cryptogenic stroke and concomitant proteinuria, none of whom were part of a hemodialysis program, and, these individuals represented 13 of 28 patients diagnosed with FD. In the present study,

the prevalence of FD was estimated to be 4.54% in patients with dual end-organ damage involving both the kidney and the brain. However, when individuals from the same lineage were included, this prevalence increased to 8.6% (only when individuals with both stroke and renal injury were considered). This highlights the practicality of screening for FD in the chronic renal failure cohort, regardless of whether the stroke is classified as cryptogenic or not.

Of the two patients diagnosed with FD in our study, one had early-stage renal disease, while the other had late-stage renal disease. This patient ultimately underwent kidney transplantation. We believe that diagnosing FD and initiating ERT in these individuals has potential benefits, including protecting the transplanted kidney and reducing the risk of further complications.

CONCLUSION

Studies examining renal dysfunction in adult stroke patients exist in the literature. However, the body of research investigating FD within this patient cohort is limited. Despite the study's limited sample size, it represents, to the best of our knowledge, the initial investigation of this issue and may serve as a foundational step toward future multicenter studies with larger and more diverse populations. Screening individuals presenting with multiple instances of end-organ damage has proven to be an effective means of promptly identifying FD cases. This approach holds particular significance for genetic counseling within affected families and for ensuring the timely provision of ERT to individuals at risk of organ failure.

Ethics Committee Approval: The study was approved by the Non-invasive Research Ethics Committee of Sakarya University (03.01.2022, 558).

Conflict of Interest: None declared by the authors.

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