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The Frequency of Fabry Disease in Patients with Cardiac Hypertrophy of Various Phenotypes Including Prominent Papillary Muscle: The TUCARFAB Study in Turkey

ABSTRACT

Background: The present study aimed to identify the frequency of Fabry disease in patients with cardiac hypertrophy of unknown etiology and to evaluate demographic and clinical characteristics, enzyme activity levels, and genetic mutations at the time of diagnosis.

Methods: This national, multicenter, cross-sectional, single-arm, observational registry study was conducted in adult patients with a clinical echocardiographic diagnosis of left ventricular hypertrophy and/or the presence of prominent papillary muscle. In both genders, genetic analysis was performed by DNA Sanger sequence analysis.

Results: A total of 406 patients with left ventricular hypertrophy of unknown origin were included. Of the patients, 19.5% had decreased enzyme activity (≤2.5 nmol/mL/h). Although genetic analysis revealed GLA (galactosidase alpha) gene mutation in only 2 patients (0.5%), these patients were considered to have probable but not "definite Fabry disease" due to normal lyso Gb3 levels and gene mutations categorized as variants of unknown significance.

Conclusion: The prevalence of Fabry disease varies according to the characteristics of the population screened and the definition of the disease used in these trials. From cardiology perspective, left ventricular hypertrophy is the major reason to consider screening for Fabry disease. Enzyme testing, genetic analysis, substrate analysis, histopathological examination, and family screening should be performed, when necessary, for a definite diagnosis of Fabry disease. The results of this study underline the importance of the comprehensive use of these diagnostic tools to reach a definite diagnosis. The diagnosis and management of Fabry disease should not be based solely on the results of the screening tests.

Keywords: Fabry disease, left ventricular hypertrophy, papillary muscles

INTRODUCTION

Left ventricular hypertrophy (LVH) is a common medical condition, particularly after the fourth to fifth decades of life and is associated with a poor long-term prognosis. Hypertension and valvulopathies account for the majority of LVH cases. Nevertheless, patients with LVH of unknown origin should be screened for treatable etiological factors.[1] Recently, several studies have identified Fabry disease (FD) as a relatively frequent cause of idiopathic LVH, the prevalence of which in middle-aged patients is 6% for males and 12% for females.[2-4]

FD, also known as Anderson-FD, is an X-linked hereditary disorder caused by lack or deficiency of lysosomal α-galactosidase (α-GLA) A enzyme activity due to the mutations in the α-galactosidase A gene (GLA – MIM No. 300644) located on chromosome Xq22[5] leading to accumulation of globotriaosylceramide (GL-3) in lysosomes in different cell types including capillary endothelial cells, arrector pili muscles, dorsal root ganglion nerves, and visceral organs.[5-7]

The cardiac variant of FD was first described in 1990. This variant can involve only the heart and is associated with some residual α-GLA activity.[8,9] Cardiac

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involvement manifests with cardiac hypertrophy in middle-aged adults and is characterized by concentric LVH accompanied by increased wall thickness.[2] Cardiac involvement in FD is seen in both genders but generally manifests later in females than in males. It is the most frequent cause of death.[6,10-15] A large registry study reported cardiac symptoms in 69% of male and 65% of female FD patients.[16] Although cardiac symptoms tend to appear later in females, they can display similar cardiac profiles. Echocardiography reveals LVH in 30%-60% of the middle-aged heterozygous women and 30%-50% of the hemizygous males with FD.[17-20]

The left ventricle (LV) papillary muscle can be involved in FD.[21] Autopsy studies in Fabry patients demonstrated hypertrophic papillary muscle[22] suggesting that a thickened papillary muscle can be considered a sign of FD and might be of diagnostic value.[11,12,15]

The facts that most of FD patients, females in particular, are diagnosed later in life when major organ involvement becomes life-threatening and that early diagnosis can prolong survival because of the availability of enzyme replacement therapy have encouraged screening studies for FD particularly in "high-risk" populations with renal failure, stroke, or LVH.

The present study aimed to identify the frequency of FD in patients with cardiac hypertrophy of various phenotypes including papillary muscle hypertrophy, as well as to evaluate demographic and clinical characteristics, enzyme activity levels, and the genetic mutations at the time of diagnosis.

METHODS

This study was designed as a national, multicenter, cross-sectional, single-arm, observational registry study without any therapeutic intervention and conducted between October 30, 2019, and February 26, 2021, in 10 participating centers, which were selected from 7 provinces (Adana, Ankara, Eskişehir, İstanbul, İzmir, Malatya, Mersin) in geographically 12 statistical regions of Turkey.

Patient selection at each study center was carried out by a cardiologist performing echocardiography on a regular basis. Patients who underwent echocardiographic examination for any reason were screened and patients of both sexes, who were at the age of ≥18 years, who had a clinical echocardiographic diagnosis of LVH (defined as septal and/or any free wall thickness ≥13 mm in end-diastole),[1] and/or presence of prominent papillary muscle (defined as a left ventricular papillary muscle [LVPM] area >3.6 cm^2 and a ratio of LVPM area/LV cavity >0.18)[21] that cannot be explained otherwise, were consecutively included in the study. Confirmed diagnosis of FD, clinical conditions such as aortic stenosis, uncontrolled hypertension (those who failed to achieve target blood pressure despite maximum treatment), valvular dysfunctions, or confirmed diagnosis of hypertrophic cardiomyopathy of sarcomeric or secondary cause, such as cardiac amyloidosis and genetic diseases other than FD, were considered the exclusion criteria. All patients who provided informed consent for their participation in the study and for blood sample collection were eligible for the study. The study was approved by Dokuz Eylül University Clinical Research Ethics Committee (date: September 12, 2019; approval no. 2019/14-01). This study was unconditionally supported by Dokuz Eylül University.

HIGHLIGHTS

- Enzymatic testing and genetic analysis alone may not be sufficient to make definite diagnosis of Fabry disease.
- Multidisciplinary approach and multiple parameters are needed in the diagnosis of Fabry disease.
- Family screening and histopathological analysis may be required in the diagnosis and treatment of Fabry disease.

Patients' data were collected during a single study visit using electronic case report forms (eCRFs). Detailed anamnesis including demographic characteristics and medical information (presence of concomitant diseases, family history of FD, presence of Fabry-related symptoms, and age at the onset of first Fabry-related symptoms) was obtained from all participants and recorded. Physical examination included measurements of body weight and height, blood pressure, and heart rate. Body mass index (BMI) was calculated for all participants and presented as the body weight in kilograms divided by the square of the height in meters (kg/m^2). In addition, echocardiographic findings such as ventricular wall thickness (mm), LV cavity area (cm^2), and LVPM area (cm^2) were also recorded.

A total of 10 mL fasting blood sample was collected from each participant for routine laboratory analysis, enzymatic analysis, and genetic testing. The blood samples were collected into tubes containing Ethylenediaminetetraacetic acid (EDTA) or into serum gel tubes. The laboratory analyses included complete blood count, blood biochemistry, and urinalysis including micro-albumin in spot urine, and 24-hour proteinuria.

Fabry patients among those with cardiac hypertrophy were identified based on α-GLA A enzyme activity levels in males and on direct genetic testing in females. In male patients, α-GLA A enzyme activity was studied using dried blood spot (DBS) samples, in which the whole blood collected from the fingertips was soaked on the filter paper (Guthrie's paper). A DBS sample with α-GLA A enzyme activity ≤2.5 μmol/L/h was subjected to genetic analysis. In both genders, genetic analysis was performed by DNA Sanger sequence analysis for the mutations in the gene coding for α-GLA A. For this purpose, only the q22.1 of chromosome X was searched.

Statistical Analysis

Statistical analyses were performed using the PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean, SD, median, and minimum–maximum for numerical variables.

RESULTS

A total of 406 patients with LVH of unknown origin were included in the study. Of 406 patients, 107 (26.4%) were

female and 299 (73.6%) were male, and the mean age was 53 ± 13 years (range: 18-90 years). Only 3 patients (0.7%) had a family history of FD. Fabry disease-related symptoms were present in 111 (27.3%) patients, with neuropathic pain (10.1%) being the most frequent symptom followed by gastrointestinal symptoms (8.9%), dyspnea (8.9%), hypersensitivity to heat and cold (8.6%), dyshidrosis (7.9%), and proteinuria (7.1%). The median (minimum–maximum) age at the onset of the first Fabry-related symptoms was 2.7 months (range, 0-245.6 months). More than half of the patients had comorbid conditions with hypertension (54.2%) being the leading, followed by diabetes mellitus (28.3%). The clinical characteristics of the patients are presented in Table 1.

Overall, the mean BMI was 28.79 ± 5.13 kg/m^2, the mean systolic blood pressure and diastolic blood pressure were 131.62 ± 18.27 mm Hg and 76.33 ± 11.14 mm Hg, respectively, and the median heart rate was 74 bpm (range, 41-110 bpm).

Echocardiographic examination demonstrated a median LV septal wall thickness of 15 mm (minimum–maximum, 13-48 mm) and a median LV posterior wall thickness of 13 mm (minimum–maximum, 4.7-60 mm). The median LVPM area (parasternal short axis view) was 3 cm^2 (minimum–maximum, 1-4.5 cm^2). Accordingly, 1 (0.2%) patient had prominent papillary muscle. Echocardiographic data are demonstrated in detail in Table 2.

The α-GLA A enzyme activity level was evaluated in 298 (73.4%) male patients, and the median level was found to be 3.7 nmol/mL/h (range: 1-12.6 nmol/mL/h). While 80.5% of these patients (240 out of 298 patients) had normal enzyme activity, 19.5% (58 out of 298 patients) had decreased enzyme activity (≤2.5 nmol/mL/h). Genetic analysis, which was performed in male patients with α-GLA A enzyme activity ≤2.5 nmol/mL/h and in all of the female patients, revealed GLA gene variants in only 2 patients (0.5%), of whom 1 was

Table 1. Clinical Characteristics of the Study Participants

	n (%)
Fabry-related symptoms	
Neuropathic pain	41 (10.1)
Gastrointestinal symptoms	36 (8.9)
Dyspnea	36 (8.9)
Hypersensitivity to heat and cold	35 (8.6)
Dyshidrosis	32 (7.9)
Proteinuria	29 (7.1)
Chronic renal failure	28 (6.9)
Hearing impairment	17 (4.2)
Young/recurrent stroke	12 (3.0)
Hemodialysis	9 (2.2)
Facial dysmorphism	2 (0.5)
Other medical conditions	
Hypertension	220 (54.2)
Diabetes mellitus	115 (28.3)
OSAS	22 (5.4)
Pacemaker	19 (4.7)
Chronic rheumatic disease	14 (3.4)
COPD	12 (3.0)
Malignancy	6 (1.5)

COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome.

Table 2. Echocardiographic Data of the Study Participants

	n	
LVSWT, mm	406	15 (13-48)
LVPWT, mm	404	13 (4.7-60)
LVESD, mm	224	30 (16-54)
LVEDD, mm	402	47 (30-69)
LAD, mm	401	40 (27-66)
ARD, mm	388	30 (20-54)
ARD, mm, ≥40 mm	388	17 (4.4)
RVD, mm	235	26 (9-53)
RVWT	34	3 (2-9)
LVPM area (parasternal short axis view), cm^2	24	3 (1-4.5)
Papillary hypertrophy	406	1 (0.2)
Mitral valve regurgitation	406	
Moderate		64 (15.8)
Severe		1 (0.2)
Mitral stenosis	406	1 (0.2)
Tricuspid valve regurgitation	406	
Moderate		39 (9.6)
Severe		2 (0.5)
Aortic valve regurgitation	406	
Mild		97 (24)
Moderate		16 (4)
Aortic stenosis	403	
None		401 (99.5)
Mild		2 (0.5)

Data are presented as n (%) or median (minimum–maximum), where appropriate.
ARD, aortic root diameter; LAD, left atrium diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVPM, left ventricular papillary muscle; LVPWT, left ventricular posterior wall thickness; LVSWT, left ventricular septal wall thickness; RVD, right ventricular diameter; RVWT, right ventricular wall thickness.

Table 3. α-GLA A Enzyme Activity, Lyso Gb3 Level, and Genetic Mutation(s)

	n	
α-GLA A enzyme activity level (nmol/mL/h)	298	3.7 (1-12.6)
Normal		240 (80.5)
Low (≤2.5 nmol/mL/h)		58 (19.5)
Genetic mutation	127	
Yes		2 (1.5)
No		125 (98.5)
Lyso Gb3 level (ng/mL)	2	0.58 (0.5-0.66)

Data are presented as n (%) or median (minimum–maximum), where appropriate.
α-GLA A, α-galactosidase A.

Table 4. Characteristics of 2 Patients with Genetic Mutation

Patient	Age/Sex	α-GLA A Enzyme Level (nmol/mL/h)	Lyso Gb3 Level (ng/mL)	Type of Genetic Mutation	LVSWT (mm)	LVPWT (mm)	eGFR mL/min/1.73 m^2
1	61/F		0.66	c.376A>G (rs149391489) (p.S126G)	22.0	15.0	54
2	49/M	2.5	0.50	c.937G>T (rs28935490) (p.D313Y) Hemizygous	20.0	16.0	48

eGFR, estimated glomerular filtration rate; F, female; LVPWT, left ventricular post-wall thickness; LVSD, left ventricular septal wall thickness; M, male; α-GLA A, α-galactosidase A.

hemizygous for a GLA gene variant. The lyso Gb3 level studied in these 2 patients was within the normal range (0.58 ng/mL and 0.66 ng/mL, respectively) (Tables 3 and 4).

DISCUSSION

In this national, multicenter, cross-sectional, single-arm observational study, which investigated the frequency of FD in a cohort of LVH patients of unknown etiology, 3 (0.7%) patients had a family history of FD and more than one-fourth of LVH patients (n = 111, 27.3%) had an FD-related symptom. Although a low α-GLA A enzyme activity level was detected in 19.5% of the patients, only 2 of them had GLA variants (0.5%). However, none of the patients (0%) had definite diagnosis of FD because the genetic analysis showed variants of unknown significance (VUS) and the lyso Gb3 levels were within the normal range. Nevertheless, lyso Gb3 levels can be normal, especially in female Fabry patients. In such cases, the definite diagnosis of FD is possible only by histopathological examination. However, due to invasive nature of this analysis, patients may reject these procedures and reaching a definite diagnosis may be impossible in those patients. More than one-fourth of LVH patients (n = 111, 27.3%) had an FD-related symptom; with neuropathic pain (10.1%) being the most frequent symptom followed by gastrointestinal symptoms (8.9%), dyspnea (8.9%), hypersensitivity to heat and cold (8.6%), dyshidrosis (7.9%), and proteinuria (7.1%). This relatively high frequency of Fabry-related symptoms in a group with no definite diagnosis of FD points out that, Fabry-related symptoms are usually very nonspecific. This is a challenging point in diagnosing FD, especially in adults who usually lack pathognomonic skin lesions. As long as organ involvement should be demonstrated in adult Fabry patients, nonspecific characteristics of Fabry-related symptoms make organ biopsies obligatory for final diagnosis, in majority of patients with a suspicion of FD.

Our results suggest that enzyme analysis or genetic analysis alone is not sufficient to make definite diagnosis of FD as these 2 tests are screening tests. Therefore, family history, clinical history, physical examination, enzyme testing, genetic testing, and lyso Gb3 level and/or histopathological examination, when necessary, should be considered altogether to make definite diagnosis of FD. As Fabry is a progressive disease and early diagnosis is extremely valuable, it is of critical importance to complete these diagnostic steps in every patient when needed.

FD is a progressive, genetic disease affecting numerous organs in both genders. The diagnosis of FD is usually delayed because clinical manifestations of the disease are similar to those seen in various diseases; thus, both the diagnosis and differential diagnosis of the disease require multidisciplinary approach.[23] Delayed diagnosis is an important risk as the disease is progressive and can result in life-threatening renal, cardiac, and neurological conditions. Fabry disease is suspected based on the patient's clinical, medical and family history and then needs to be confirmed by detection of low/no α-GLA A enzyme activity level and/or specific mutations in GLA gene and/or histopathology. In addition, the diagnosis can be supported by high levels of lyso Gb3.[24]

While there is no or little enzyme activity in males, females may show normal or low-normal enzyme activity, thereby females should be directly subjected to genetic testing to diagnose the disease.[25] Cardiac manifestations including LVH are common in FD patients and appear later in females than males and females who usually present with cardiac symptoms alone.[1]

LVH, usually concentric, is the most common late manifestation of cardiac FD with the prevalence reported in 50% of males and 30% of females affected by the disease.[19] Moreover, Fabry GLA gene pathogenic variants have been detected in nearly 4% of individuals with LVH of unknown etiology[26] and therefore should be ruled out as a differential diagnosis.

Along with the availability of enzyme replacement therapy, screening of specific cohorts to early identify FD patients has gained importance. Accordingly, the prevalence of FD among patients with LVH or with hypertrophic cardiomyopathy has been studied in numerous studies and reported in a range from 0.3% to 12%.[2-4,27-31] These significantly different results between the studies might have arisen from the differences in the populations screened, study designs, and methods used to detect FD.

In 2 single-center studies from Turkey, the ratio of FD among patients with idiopathic LVH was 1.05% and 2.5%, respectively.[32,33]

In these studies, a low α-GLA A enzyme activity level was detected in 3.0% of 230 patients with LVH.[2] Likewise, low α-GLA A enzyme activity was reported in 3.9%,[3] 1%,[34] and 0.5%[27] of the patients with hypertrophic cardiomyopathy.

Given that α-GLA A enzyme activity level is a strong indicator of FD in males, it was studied only in male patients in the present study, and the median activity level was found to be 3.7 (1-12.6) nmol/mL/h. Although 19.5% of these patients had

low levels of enzyme activity, the levels were higher than those found in the previous studies. This may be due to the fact that α-GLA A enzyme activity in such studies was studied only in male patients.

The diagnosis of FD should be confirmed directly by genetic analysis in females and after detecting no or deficient α-GLA A enzyme activity in males. Today there are more than 900 GLA gene variants (Human Gene Mutation Database, www.hgmd.org). However, not all individuals with variants of the GLA gene develop manifestations of FD. Some of these variants may be considered polymorphisms, e.g. individual variability, while others may or not be associated with manifestations of FD and have been considered by the scientific community as GVUS.[35]

In 2 studies, pathogenic GLA gene variants were detected in 2/7 and in 5/15 cases with low enzyme activity, respectively,[2,34] whereas, in another study,[3] diagnosis of FD was confirmed by genetic testing in all of the patients with low enzyme activity. In a cohort of 34 women with hypertrophic cardiomyopathy, Chimenti et al[4] investigated diagnostic histologic features of FD based on biventricular endomyocardial biopsy and plasma α-GLA A enzyme activity and found pathogenic GLA gene variants in 4 (12%) patients, which is significantly higher than that found in the above-mentioned studies.

In the present study, GLA genetic analysis, which was performed in male patients with low enzyme activity and in all female patients, revealed pathogenic gene variants in only 2 patients (0.5%), the c.937G>T(rs28935490)(p.D313Y) for the hemizygous male and the c.376A>G (rs149391489) (p.S126G) for the heterozygous (?) female. These mutations were classified in the databases (reference) as VUS. Given that these 2 patients had remarkable LVH and low glomerular filtration rate at such a young age, we thought FD should not be excluded in these patients despite normal lyso Gb3 levels and VUS genotypes. Thus, the patients were diagnosed with possible FD. In order to reach a definite diagnosis and to decide whether enzyme replacement therapy is necessary, further evaluation including family screening and histopathological examination of the biopsies from the heart and/or kidney were planned in these patients, but the patients refused to undergo further analysis.

Similarly to the results of the present study, Ommen et al.[36] who investigated 100 consecutive patients that had undergone subaortic ventricular septal myectomy for the treatment of hypertrophic cardiomyopathy, could not find any patients with FD. They concluded based on their results that FD is unlikely among patients with severely symptomatic, obstructive, asymmetrical basal septal hypertrophy.

Study Limitations

Although this is the first multicenter study investigating the frequency of FD in a cohort of LVH patients in Turkey, small sample size is the major limitation of the study. Although the main aim of the study was to find out the prevalence rate for FD among LVH patients through a standard screening method, we were unable to reach a definite diagnosis in 2 patients with low enzyme levels and positive genetic tests due to the need for invasive tests. This is a common issue in population screening studies because invasive tests are frustrating for asymptomatic patients. As long as there was no patient with a definite diagnosis of FD, we could not analyze the predictive value of Fabry-related signs and symptoms in the diagnosis of FD.

CONCLUSION

The literature data about the prevalence of FD among patients with LVH of unknown etiology shows a great variation; ranging from 0.3% to 12%.[2-4,27-31] This difference is due to the characteristics of the population screened and also according to the definition of disease used in these trials. From a cardiology perspective, LVH is the major reason to consider screening for FD. Although enzyme analysis is the primary tool for screening, it is not enough to make a definite diagnosis. Enzyme testing, genetic analysis, substrate analysis, histopathological examination, and family screening should be performed, when necessary, for definite diagnosis of FD. The results of this study underline the importance of comprehensive use of these diagnostic tools and family history to reach a definite diagnosis. The diagnosis and management of FD should not be based solely on the results of limited parameters used in screening tests.

Ethics Committee Approval: The study was approved by Dokuz Eylül University Clinical Research Ethics Committee (date: September 12, 2019; approval no. 2019/14-01).

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