Ratio of Fabry disease in patients with idiopathic left ventricular hypertrophy: A single-center study in Turkey

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Objective: Fabry disease (FD) is a progressive, X-linked inherited disorder of glycosphingolipid metabolism which arises due to deficient or absent activity of lysosomal α-galactosidase A (α-Gal A). This may be associated with increased left ventricular (LV) wall thickness and may mimic the morphological features of hypertrophic cardiomyopathy. The purpose of this study was to define the ratio of occurrence of FD to the manifestation of unexplained left ventricular hypertrophy (LVH).

Methods: We studied a prospectively assembled a consecutive cohort of 190 patients with unexplained LVH on echocardiography. The criterion for LVH diagnosis was a maximum LV wall thickness of 13 mm or greater. All patients were tested for mutations in the GLA gene.

Results: The majority of patients were male (n=119, 63%) and the mean patient age was 47.2±15 years. In 190 patients diagnosed with LVH, we identified 2 patients (1.05%) with documented GLA mutations [c.427G>A (p.A143T)(p.Ala143Thr)] and [c.937G>T (p.D313Y)(p.Asp313Tyr)]. After the family screening, 3 additional patients with FD were identified in 2 families, including 5 individuals who are now receiving enzyme replacement therapy.

Conclusion: We identified 2 index patients with FD and unexplained LVH. Cardiologists should, therefore, be aware of FD in cases of unexplained LVH. Family screening is crucial for the earlier identification of unaffected new patients who may benefit from enzyme replacement therapy. (Anatol J Cardiol 2020; 23: 79-85)

Keywords: hypertrophic cardiomyopathy, echocardiography, Fabry disease

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes that is characterized by cardiac hypertrophy and is unexplained by flow-limiting coronary artery disease, abnormal loading conditions, a non-dilated left ventricle, and a normal or increased ejection fraction. Autosomal recessive and X-linked modes of inheritance have been described, but are rare (1, 2).

Fabry disease (FD) is an X-linked inherited disorder of metabolism that occurs due to mutations in the GLA gene that encodes α-galactosidase A (α-Gal A), a lysosomal enzyme, which results in progressive, systemic sphingolipid accumulation with characteristic clinical findings (3-10). The predominant causes of significant morbidity and mortality are cardiac, renal, and cerebrovascular disease (4). Left ventricular hypertrophy (LVH) is the most frequent cardiac sign (11). Men (usually from 30 years of age) and women (usually from 40 years of age) most often present with unexplained LVH that is usually concentric and non-obstructive, but sometimes may mimic sarcomeric HCM (12). FD is phenotypically heterogeneous; the spectrum of organ involvement ranges from multiple organ findings (Classic FD) to isolated organ involvement (as in the cardiac or late-onset variant of FD (4)).

The worldwide incidence of FD is reported to range between 1/40,000 and 1/117,000 (13), with neonatal screening studies suggesting an incidence of 1/4.100 and 1/3.100 (14, 15). However, further studies suggested that many of these are late-onset variations, polymorphisms, or non-disease forming factors. A
higher incidence of FD was reported in specific populations, such as patients with LVH, chronic kidney disease, and stroke occurrence at a young age (16). The ratio of FD in screening studies performed in various populations around the world has been reported at different proportions (Table 1) (17-31). The aim of this study is to determine the ratio of occurrence of FD using echocardiography in patients with unexplained left ventricular hypertrophy.

**Methods**

A total of 190 consecutive patients with unexplained LVH (maximum LV wall thickness ≥13 mm) diagnosed by echocardiography between May 2018 and May 2019 were included in this study. The diagnosis of HCM was based on the echocardiographic demonstration of unexplained LVH, i.e., maximum LV wall thickness is 15 mm in at least one myocardial segment as suggested by the ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy (1). Genetic and non-genetic disorders can present with lesser degrees of wall thickness (13-14 mm), however, in these cases, the diagnosis of HCM requires evaluation of other features, such as family history, non-cardiac symptoms and signs, electrocardiogram (ECG) abnormalities, laboratory tests, and multi-modality cardiac imaging (2). To establish a confirmed diagnosis of HCM, it is required that the presence of LVH be unexplained by abnormal loading conditions (1, 2). Patients with arterial hypertension were excluded when hypertension was associated with mild LVH (LV mass/BSA <109 g/m² (women) and <132 g/m² (men), regardless of the stage of hypertension (28). Patients with hemodynamically significant valvular heart disease, other loading conditions (aortic stenosis, coarctation, and previous diagnosis of FD), and those having a previous history of any disease known to be associated with LVH and familial history of autosomal dominant HCM or FD were also excluded. Written informed consent was obtained from all participants. The study was performed with adherence to the Helsinki Protocol and the study design was approved by the Local Ethics Committee.

Evaluation of patients included medical history, clinical examination, and 12-lead electro- and echocardiography. Trans-thoracic echocardiography (TTE) (Philips Healthcare, Andover, }

| Author et al. | Year | Country | LVH selection criteria | Sample size | Screening method | Confirmation method | Ratio of FD (%) |
|---------------|------|---------|------------------------|-------------|------------------|---------------------|-----------------|
| Nakao et al. (17) | 1995 | Japan | LVH ≥13 mm | 230 | Plasma α-Gal A activity | Genetic study | 7/230 |
| Sachdev et al. (18) | 2002 | UK | HCM ≥13 mm | 153 | Plasma α-Gal A activity | Genetic study | 6/153 |
| Ommen et al. (19) | 2003 | USA | Symptomatic HCM | 100 | | Myectomy tissue | 0/100 |
| Chimenti et al. (20) | 2004 | Italy | HCM ≥13 mm | 96 | | Endomyocardial biopsy & α-Gal A activity | 6/96 |
| Monserrat et al. (21) | 2007 | Spain | HCM ≥13 mm | 508 | Plasma α-Gal A activity | Genetic study | 5/508 |
| Havndrup et al. (22) | 2010 | Denmark | HCM ≥13 mm | 90 | | Genetic study | 3/90 |
| Elliott et al. (23) | 2011 | Europe | LVH ≥15 mm | 1,386 | | Genetic study | 7/1,386 |
| Hagège et al. (24) | 2011 | France | LVH ≥15 mm | 392 | DBSS | α-Gal A activity & Genetic study | 4/392 |
| Mawatari et al. (25) | 2013 | Japan | LVH ≥13 mm | 738 | Serum α-Gal A activity | Genetic study | 0/738 |
| Terryn et al. (26) | 2013 | Belgium | LVH ≥13 mm | 560 | DBSS | Genetic study | 5/560 |
| Palecek et al. (27) | 2014 | Czech | HCM ≥13 mm | 100 | DBSS or plasma α-Gal A activity | α-Gal A activity & Genetic study | 4/100 |
| Baptista et al. (28) | 2015 | Portugal | LVMI ≥96 g/m² women, ≥116 g/m², for men | 47 | DBSS | Genetic study | 1/47 |
| Vieitez et al. (29) | 2018 | Spain | Clinical symptom or sign associated to FD | 805 | DBSS | Genetic study | 21/805 |
| Maron et al. (30) | 2018 | USA | HCM ≥13 mm | 585 | DBSS | Genetic study | 2/585 |
| Kim et al. (31) | 2019 | Korea | LVH ≥13 mm | 988 | Plasma α-Gal A activity | Genetic study | 5/988 |

LVH - left ventricular hypertrophy; α-Gal A - α-galactosidase A; HCM - hypertrophic cardiomyopathy; DBSS - dry blood spot screening
Massachusetts, USA) was used to evaluate the parasternal and apical angles (2D, M-mode, Doppler echocardiography), with the patient placed in the left lateral decubitus position after at least 15 minutes of rest. Echocardiographic images were obtained in all 4 standard views (long-axis parasternal, short-axis parasternal, two-chamber apical, and four-chamber apical) using the techniques recommended by the American Society of Echocardiography guidelines (32). From the parasternal long-axis view of the LV end-diastolic and end-systolic diameters, interventricular septal and posterior wall thicknesses were expressed in millimeters. Left ventricular ejection fraction was calculated from 4 apical chamber views by manually tracing the end-diastolic and end-systolic endocardial borders using Simpson’s method. The myocardial function of FD-diagnosed patients was assessed via myocardial deformation analyses of two-dimensional speckle tracking echocardiography (2D STE). End-diastole was defined as the peak of the R-wave in the electrocardiogram and end-systole was defined as closure of the aortic valve. Endocardial borders were detected at the 2D end-systole. In case a correction was needed due to false auto-tracking, manual adjustments were made to ensure correct tracking, or the width of 2D STE was arranged for full coverage of the LV wall. Global longitudinal strain analysis was performed from apical 4-chamber, 2-chamber, and apical 3-chamber images for global longitudinal strain. The Philips Epiq 7C QLAB-CMQ software program was used to perform the analysis. Peak systolic strain measurements in each segment were performed automatically via a software (analysis) program. In total, individual longitudinal strain values of 18 segments were obtained and the mean value was determined as global strain. Segments that could not be traced after manual adjustment by the operator were excluded.

Screening for FD in all patients was performed by mutation analysis. Peripheral venous blood samples were collected in EDTA tubes (2 mL) from each patient, blinded, and sent to an external laboratory that specializes in the diagnosis of genetic diseases. In all patients GLA gene sequence analyses were carried out while the levels of α-Gal A enzyme activity and lysogb3 were measured in patients with GLA gene mutations. Family screening was performed in patients with gene mutation.

Mutation analysis-polymerase chain reaction-sequencing

In terms of genotype analysis, GLA gene sequence analysis was performed. The seven exons of the GLA gene were amplified by polymerase chain reaction (PCR) with specific primers and sequenced by the Sanger method on a genetic analyzer (Applied Biosystems Inc. CA, USA). Results were analyzed using the software SeqScape 2.5.0 (Applied Biosystems Inc. CA, USA). DNA was extracted with an QIAamp DNA Blood Mini Kit (Qiagen Inc.).

A total of 7 pairs of PCR primers were designed to amplify the 7 exons encoding the GLA gene (29). The PCR amplifications were carried out using Taq DNA polymerase (Phirell HS, Thermo Inc.) and a PCR protocol was set, having an initial hold of 1 minute at 95°C, 45 cycles (of 10 seconds at 95°C, 10 seconds at 60°C and 20 seconds at 72°C), and a final extension of 1 minute at 72°C. After the thermal cycle protocol for PCR, the product was checked using 2% agarose gel electrophoresis. PCR products were purified using the ZR-96 DNA Sequencing Clean-up Kit (Zymo Research Corp.) and the purified products were sequenced bidirectionally on an ABI 3130 capillary gel electrophoresis system (Applied Biosystems Inc. CA, USA) according to the manufacturer’s protocol. The exons of the gene and the exon-intron connections were analyzed by the SeqScape 2.5.0 (Applied Biosystems Inc. CA, USA) software and the sequence variations were determined.

α-Gal A activity testing

Determination of AGE activity was based on dried blood spot test, for which an AGE activity study was carried out using the fluorimetric method (30). The substrate was α-D-galactopyroniside (Toronto Research Chemicals; Catalog no: M334475) and N-Acetylgalactosamine (Sigma-Aldrich; A2795) was the inhibitor. Incubation was carried out at 37°C for 17 hours with a 3 mm DBS punch, inhibitor, and substrate. Fluorescence was recorded using excitation wavelength of 366 nm and emission wavelength of 442 nm with the fluorimeter (BioTek Synergy). The calibration curve was generated with 4-methylumbelliferone (Sigma-Aldrich; M1381) to evaluate the results. Normal range of α-Gal A activity was defined as ≥3.3 μmol/L/hour. This cut-off point was determined by the receiver operating characteristic testing by the Duzen Laboratory group.

Lyso-globotriaosylsphingosine (lyso-Gb3)

It is analyzed by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) system. A 5 mm DBS punch is taken from standards, controls, and samples and internal standard N-Gly-Lyso-Gb3 is added. The extraction process is then taken into vials and analyzed in the 10 μL LC-MS/MS system.

Statistical analysis

The demographic characteristics and echocardiographic parameters of all screened patients were analyzed. Data were submitted to descriptive analysis using the Statistical Package for the Social Sciences (SPSS) program, version 19.0 (SPSS Statistics IBM®), and were expressed as numbers or percentages or mean values±standard deviation.

Results

We screened 190 patients with unexplained LVH. A majority of the patients were male (n=119, 63%) and the mean age was 47.2±15 years. Two genetically confirmed patients (2 women) were identified (1.05%).

Patients with FD

The clinical characteristics of these two patients and the results of genetic analysis are shown in Table 2. After the initial
diagnosis of FD, all patients were referred to a metabolic disease specialist for follow-up, treatment, pedigree analysis, and genetic counseling.

Patient 1: A 58-year-old female patient with a diagnosis of recurrent cerebrovascular disease (stroke) was referred to the cardiology department for transthoracic echocardiographic evaluation. She also had hypertension and chronic kidney disease stage 3b (glomerular filtration rate 42 mL/min/1.73 m²). She had a family history of dialysis (mother and maternal aunt). Systemic arterial pressure was 144/92 mm Hg, heart rate was rhythmic and was recorded at 84 beats/minute. Electrocardiography showed normal sinus rhythm. Transthoracic echocardiography demonstrated left ventricular hypertrophy with a maximum septal wall thickness of 13 mm. The patient had diastolic dysfunction (grade I) and low systolic tissue Doppler velocities in the basal segment of the septum (6.8 cm/s). Global longitudinal strain was reduced (-10.5%), with a preserved left ventricular ejection fraction (60%) (Fig. 2). She showed normal α-Gal A activity (3.1 μmol/L/hour - reference value ≥2.5 μmol/L/hour) and lysosomal β3 rate (1.12 ng/mL - reference value ≤1.3 ng/mL) (Table 2). Molecular analysis for FD resulted as [c.937G>T (p.D313Y)(p.Asp313Tyr)]. Further clinical assessment was carried out following the final diagnosis. She had no angiokeratomas and the eye examination was normal. Elevated levels of urea and creatinine was detected in urine analysis. Proteinuria was detected in urine analysis. A daughter and a son having the same mutation were revealed by family screening. Enzyme replacement therapy was initiated for all patients.

Patient 2: A 55-year-old female patient was referred to the cardiology outpatient clinic for echocardiographic assessment. She had chronic kidney disease Stage 3a (glomerular filtration rate 54 mL/min/1.73 m²). The patient had no symptoms until she was 30 years of age, after which fatigue, weakness, and palpitation started. Functional capacity was New York Heart Association II at the time of evaluation. Systemic arterial pressure was 122/72 mm Hg, heart rate was rhythmic and was recorded at 84 beats/minute. Electrocardiography showed normal sinus rhythm. Transthoracic echocardiography demonstrated left ventricular hypertrophy with a maximum septal wall thickness of 13 mm. The patient had diastolic dysfunction (grade I) and low systolic tissue Doppler velocities in the basal segment of the septum (6.8 cm/s). Global longitudinal strain was reduced (-10.5%), with a preserved left ventricular ejection fraction (60%) (Fig. 2). She showed normal α-Gal A activity (3.1 μmol/L/hour - reference value ≥2.5 μmol/L/hour) and lysosomal β3 rate (1.12 ng/mL - reference value ≤1.3 ng/mL) (Table 2). Molecular analysis for FD resulted as [c.937G>T (p.D313Y)(p.Asp313Tyr)]. Further clinical assessment was carried out following the final diagnosis. She had no angiokeratomas and the eye examination was normal. Elevated levels of urea and creatinine was detected in urine analysis. Proteinuria was detected in urine analysis. A daughter and a son having the same mutation were revealed by family screening. Enzyme replacement therapy was initiated for all patients.

**Table 2. Clinical characteristics and genetic results of patients with Fabry disease**

| Patient 1 | Patient 2 |
|-----------|-----------|
| Gender    | Female    | Female    |
| Age (years)| 58        | 55        |
| Pattern of LVH | Concentric | Concentric |
| Interventricular wall thickness (mm) | 20         | 13         |
| Posterior wall thickness (mm) | 20         | 13         |
| LV end-diastolic diameter (mm) | 44         | 46         |
| LV end-systolic diameter (mm) | 28         | 31         |
| Ejection fraction (%) | 60         | 60         |
| LV mass index (g/m²) | 239        | 118        |
| Acroparesthesia | +          | +          |
| Angiokeratoma | -          | -          |
| Hypohydrosis | -          | -          |
| Corneal opacities | +          | +          |
| Proteinuria | +          | +          |
| Cerebral infarction | +          | -          |
| α-Gal A activity (μmol/L/h)* | 2.1        | 3.1        |
| Lyso-Gb3 (ng/mL)* | 1.40       | 1.12       |
| Mutations - Missense | p.A143T    | p.D313Y    |
| Nucleotide change | c.427G>A    | c.937G>T   |

*Reference value ≥2.5 μmol/L/hour. *Reference value ≤1.3 ng/mL.
LVH - left ventricular hypertrophy; LV - left ventricular; α-Gal A - α-galactosidase A; Lyso-Gb3 - globotriaosylsphingosine

**Discussion**

FD involves potentially life-threatening complications such as progressive kidney damage, hypertrophic cardiomyopathy and stroke. Diagnosis is often delayed because of a lack of awareness among clinicians about such a rare disease and because of the diversity of clinical symptoms among different ages of onset and rates of progression (33). Delay in the diagnosis and treatment can result in irreversible clinical outcomes. FD significantly reduces life expectancy (4, 11) and cardiac involvement is the leading cause of mortality in FD (11, 34). Unexplained LVH is the most common manifestation of cardiac involvement in FD and its differential diagnosis is extremely important (35). Death due to cardiovascular complications occurs usually at the ages of 55 years in men and 66 years in women (34). Predictive factors for cardiovascular events in patients with FD include older age, overall disease severity (particularly end-stage renal disease), and the presence of LVH and prolonged QRS (≥120 ms) (36).

The ratio of FD in patients with unexplained LVH has been investigated in different countries (Table 1) (17-31). The actual
incidence and ratio may be greater than expected (37). The incidence of “Classic Fabry disease” in the general population is estimated to be between 1/3,100 and 1/117,000. The incidence increases in high-risk populations, for example, FD has been reported in 0.5-1.2% of young patients with cryptogenic ischemic stroke (38). Although the incidence and prevalence of FD vary geographically, the true epidemiological data of FD is unknown due to atypical or oligosymptomatic forms (4). In previous studies of FD in patients with apparently unexplained LVH, the ratio of FD was found to vary between 1% and 12% (Table 1) (17-31). The differences between the populations screened and the screening methods used to measure α-Gal A activity may explain the different ratios reported by these studies. According to the Lyon hypothesis, inactivation of the X gene is random, therefore, FD can occur in severe forms in some women (39). However, it should be noted that women have been overlooked with α-Gal A activity screenings. In most previous ratio studies, women were excluded from the study or screened with α-Gal A activity, which may miss the diagnosis of FD in female patients (17, 18, 25, 27). Therefore, in our study, we screened all patients with mutation analysis.

In Turkish populations, patients with nephropathy have usually been included in studies on the ratio of FD. However, a few studies have also been conducted with patients who have undergone kidney transplantation. Okur et al. (40) performed screening for FD in patients with hemodialysis by using an α-Gal
A assay on dried blood spots with a filter paper test, and they identified two FD patients out of 1136 (0.17 %). Yalın et al. (41) identified 17 patients with FD in a group of 5657 renal transplant and dialysis patients (0.3 %). However, there is no comprehensive study on the ratio of FD in patients with unexplained LVH. In our study, we screened 190 patients with unexplained LVH, diagnosed them using echocardiography, and found FD in 1.05% of patients with LVH (including all patients with a maximum LV wall thickness of 13 mm or greater).

In our study, 2 female index cases were identified with mutation analysis. In patient 1, significant LVH (maximal wall thickness 20 mm) and right ventricular wall thickening was observed on transthoracic echocardiography. Delayed cardiac enhancement was demonstrated by cardiac magnetic resonance imaging. The activity of α-Gal A (2.1 μmol/L/hour) was low and the lysoGb3 level was high (1.40 ng/mL) in the laboratory analysis (Table 2). A [c.427G>A (p.A143T) (p.Ala143Thr)] mutation, consistent with the diagnosis of FD, was documented by genetic testing. A daughter and a son having the same mutation were revealed by family screening. In patient 2, concentric left ventricular hypertrophy and a maximum septal wall thickness of 13 mm was demonstrated by transthoracic echocardiography. She had normal α-Gal A activity and her lysoGb3 levels were also normal. Molecular analysis for FD resulted as [c.937G>T (p.D313Y) (p.Asp313Tyr)]. Elevated levels of urea and creatinine (end-stage renal disease) were detected in the biochemical analysis. Family screening tests showed that her sister also had the same mutation.

Due to the systemic involvement of FD, a multidisciplinary approach is required in the management of organ specific complications. Many different medical specialists are often involved in diagnosis, including nephrologists 14%, genetic experts 10%, pediatricians 8%, dermatologists 7%, family physicians 5%, cardiologists 5%, and other physicians 51% (9, 42). The difference between clinicians is largely due to the variety and non-specificity of the symptoms, and unfortunately, more than 25% of patients are misdiagnosed. Due to the lack of specificity of symptoms, the diagnosis of FD is often delayed by a mean duration of 12-16 years from the onset of symptoms to the time of diagnosis (9). Screening studies for FD in high-risk groups are recommended and have important effects, namely; (1) the detection of FD in an undiagnosed patient provides appropriate management for the index patient, (2) family screening is important for the earlier identification of new FD–affected patients who may benefit more from enzyme replacement therapy, (3) appropriate genetic counseling can be provided to these patients, and (4) the disease can be prevented by prenatal screening (43).

Study limitations

Our data was derived from a single center, and the sample size was relatively small as compared to other studies. However, screening for FD in our country remains suboptimal. Therefore, a further study on a large and multi-center cohort is needed.

Conclusion

In conclusion, FD is a rare and progressive disease that involves potentially life-threatening complications. Cardiologists should, therefore, be aware of FD in cases of unexplained LVH. FD can be identified by systematic screening of HCM patients in specific populations, such as patients with chronic kidney disease and/or LVH and/or stroke.

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