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Original Article

Evaluation of echocardiographic findings of fabry patients: A single center experience

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Abstract

Aim: Fabry disease is a lysosomal storage disease caused by α-galactosidase A enzyme deficiency due to mutation in the GLA gene with X-linked transition. Fabry disease may present with skin, eye, kidney, cardiac and neurological system involvement. Cardiovascular findings are important in terms of mortality due to differences in clinical presentation and difficulties in diagnosis. Cardiac involvement is the most common cause of mortality, therefore echocardiographic evaluation is important at baseline. Echocardiographic examination is a noninvasive and effective diagnostic method for the evaluation of cardiac involvement during both diagnosis and follow-up.

Material and Methods: Echocardiographic findings of 18 patients who were followed up in the outpatient clinic for Fabry disease between August 2018 and December 2019 were retrospectively evaluated. All patients were evaluated for cardiac involvement by 2-dimensional echocardiography.

Results: Between August 2018 and December 2019, there were 18 Fabry patients who were followed up in our hospital. In our study, 13 patients were female and 5 were male. The mean age was 42.2 ± 13.5 years. 12 patients with enzyme replacement therapy had different system involvement; Seven had cardiac involvement by echocardiography. The cardiac involvement rate of our symptomatic patients receiving treatment was 58.3% (7/12). Seven patients with cardiac involvement; Six (85.7%) had non-obstructive hypertrophic cardiomyopathy and stage 1 diastolic dysfunction in the left ventricle.

Conclusion: In Fabry disease, cardiovascular findings are the most important cause of mortality and early diagnosis is important. The most common echocardiographic findings in our patient group were non-obstructive hypertrophic cardiomyopathy (85.7%) and left ventricular diastolic dysfunction. In the presence of unexplained non-obstructive hypertrophic cardiomyopathy, Fabry disease should be considered in the differential diagnosis. Fabry disease have multisystemic involvement, it requires absolute multidisciplinary approach in the diagnosis and follow-up of patients.

Keywords: Fabry disease; echocardiography; left ventricular hypertrophy

INTRODUCTION

Fabry disease is a lysosomal storage disease caused by mutations in the GLA gene, showing an X-linked transition. The deposition of glycosphingolipids (such as globotriaosylceramide-Gb3) due to a decrease in enzim α-galactosidase A (α-Gal-A) enzyme activity occurs in many tissues in the body such as skin, eye, heart, kidney, brain, vascular and nervous system and especially in vascular endothelium (1). Symptoms may vary depending on age and gender. Because of X-linked inheritance, men tend to develop more and more serious symptoms. The clinical presentation of the patients is heterogenous and angiokeratoma, corneal changes, peripheral neuropathy, gastrointestinal symptoms, renal disease, cardiovascular disease and cerebrovascular events can be seen (2,3). In the diagnosis of the disease, additional evaluations such as α-Gal-A enzyme activity level, genetic analysis of GLA gene, plasma / urine Gb3 level and biopsy may be required (3).

Fabry disease may present with two main phenotypes; There are significant differences in classical and variant, clinical presentations (2). Cardiovascular findings are an important determinant of mortality in the disease, which is difficult to diagnose due to clinical differences. Echocardiography is a noninvasive and effective method that provides structural and functional evaluation of

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the heart (4). Although increased left ventricular wall thickness is the predominant presentation of the disease, atrial dilatation, valve thickening, aortic root dilatation, atrial and ventricular dysfunction, and arrhythmia may occur (4). Cardiac findings in Fabry's disease are initially symmetrical and concentric left ventricular hypertrophy followed by localized thinning of the basal posterior wall and progressive cardiac dysfunction.

Many complications can be prevented in Fabry disease by early diagnosis and early treatment. Early enzyme replacement therapy (ERT) prevents the development of cardiac fibrosis. Therefore, in the presence of unexplained left ventricular hypertrophy on echocardiography, Fabry disease should be considered in the differential diagnosis.

The aim of this study was to evaluate the cardiac involvement of patients with Fabry disease by echocardiography.

MATERIAL and METHODS

Echocardiographic evaluations of patients who were followed up in the outpatient clinic with the diagnosis of Fabry disease between August 2018 - December 2019 were included in the study retrospectively. Patients who did not attend regular follow-up were excluded from the study. Written informed consent was obtained from all participants. The study was performed with adherence to the Helsinki Protocol and approved by the local Ethics Committee. Evaluation of patients included medical history, clinical examination, and echocardiography. Echocardiographic evaluation was performed using Philips Epiq 7 echocardiography machine and X5 transducer (Philips Healthcare, Andover, Massachusetts, USA). Echocardiographic measurements were made from standard parasternal long axis, short axis, apical two and four chamber views in the left lateral decubitus position. All patients performed standard two-dimensional and color doppler echocardiographic examination. The interventricular septum and posterior wall thickness, left ventricle end-systolic and left ventricle end-diastolic diameters, left atrial and aortic diameters were measured from the parasternal long axis view in millimetres. Left ventricular ejection fraction was calculated from the apical four-chamber and two-chamber images by the modified Simpson method. Conventional echocardiographic measurements were done according to the American Society of Echocardiography guidelines.

RESULTS

In our study, 18 patients diagnosed as Fabry disease and 13 of them were female and 5 of them were male. The mean age of the patients was 42.2 ± 13.5 years. All patients had α-Gal-A enzyme level, Gb3 level and genetic analysis. Genetic analyzes of patients include mutations identified as polymorphism, previously reported pathogenic mutations, and new pathogenic mutations. Six of the patients had no system involvement and these patients were followed up regularly without enzyme replacement therapy. 12 patients (8 females, 4 males) receiving enzyme replacement therapy had different system involvement at different stages.

Table 1. Echocardiographic findings of patients with cardiac system involvement

Case	Gender	Age (years)	Acroparesthesia/ neuropathy	Renal involvement	Cardiac involvement	Echocardiographic findings	GLA gene analysis
1	Female	58	+	+	+	LVH, LV diastolic dysfunction grade 1	c.427G>A (p.A143T) (p.Ala143Thr) heterozygous
2	Female	46	-	+	+	LVH, LV diastolic dysfunction grade 1	IVS3+4A>G (c.547+4A>G) heterozygous
3	Female	56	+	+	+	LVH, LV diastolic dysfunction grade 1	c.937G>T (p.D313Y) (p.Asp313Tyr) heterozygoust
4	Male	29	-	+	+	LVH	c.708G>A (p.W236*) hemizygous
5	Female	58	+	+	+	LV diastolic dysfunction grade 1	c.937G>T (p.D313Y) (p.Asp313Tyr) heterozygous
6	Male	54	+	+	+	LVH, LV diastolic dysfunction grade 1	c.659G>T (p.R220L) (p.Arg220Leu) hemizygous
7	Female	55	-	+	+	LVH	c.613C>T (p.P205S) (p.Pro205Ser) heterozygous

LVH, left ventricular hypertrophy; LV, left ventricle

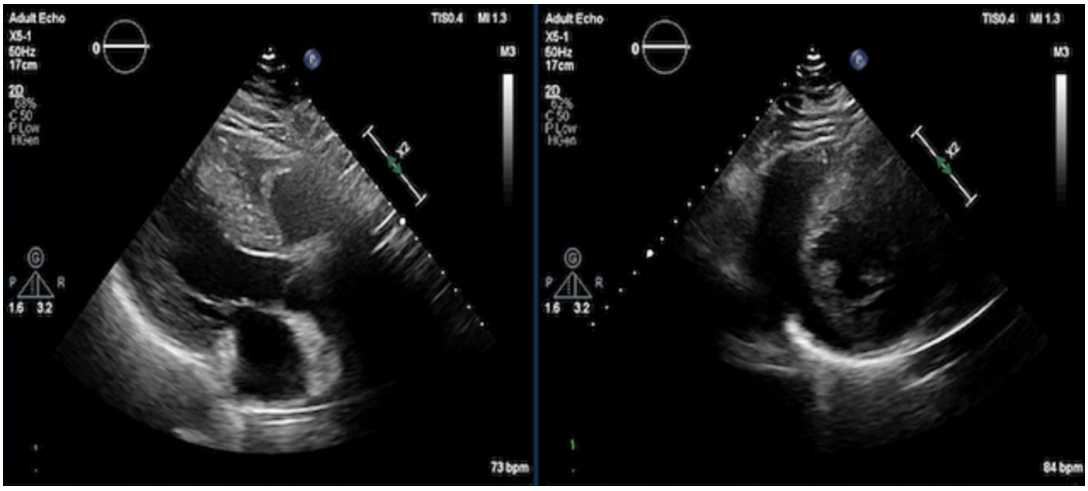

Figure 1. Transthoracic echocardiography showed concentric left ventricular hypertrophy (maximal wall thickness 20 mm) from parasternal long axis, short axis.

Seven patients receiving enzyme replacement therapy had both renal and cardiac involvement, while 3 patients had only renal involvement. Two patients had gastrointestinal system complaints (abdominal pain and diarrhea) and six had acroparesthesia. The cardiac involvement rate of the symptomatic patients receiving enzyme replacement therapy was 58.3% (7/12). In 6 of 7 patients with cardiac involvement; (85.7%) had non-obstructive hypertrophic cardiomyopathy and 5 (71.4%) had stage 1 diastolic dysfunction in the left ventricle. The most common echocardiographic findings were left ventricular hypertrophy and left ventricular stage 1 diastolic dysfunction. Echocardiographic findings and other system involvement of patients with cardiac involvement are given in Table 1 and Figure 1.

DISCUSSION

In this study we examined the role of echocardiography in patients with Fabry disease. 18 Fabry patients were included in the study and 12 patients received enzyme replacement therapy. Cardiac involvement was present in 7 (6 female, 1 male) of 12 patients receiving enzyme replacement therapy (58.3%). The most common echocardiographic finding was left ventricular hypertrophy (85.7%).

Ju WC et al retrospectively reviewed 139 Fabry patients, reported that cardiovascular involvement was 60.4%, and 84.8% of patients had concentric left ventricular hypertrophy on echocardiography (5). These results are consistent with our study. In our study, the rate of cardiac involvement was high and the most common echocardiographic finding was left ventricular hypertrophy.

The most common cause of mortality in Fabry patients is due to cardiac involvement. It is reported that 60% of patients have cardiac involvement at the time of diagnosis in Fabry patients and left ventricular wall thickness increases with age in patients not receiving treatment. Echocardiography is a non-invasive diagnostic tool and is very useful for evaluating cardiac involvement in Fabry patients. Left ventricular hypertrophy is the most common cardiac finding associated with glycosphingolipid accumulation in myocytes in Fabry patients (6). Non-obstructive hypertrophic cardiomyopathy is usually observed in Fabry disease due to myocardial involvement. In addition, aortic root dilatation, valve thickening, valve regurgitation, right ventricular hypertrophy and diastolic dysfunction can be detected by echocardiography in Fabry patients. In 50% of Fabry patients, mild to moderate regurgitation with aortic and mitral valve thickening is observed. Aortic root dilatation is not severe enough to require valve or root replacement (6).

Echocardiography plays an important role in the evaluation of left ventricular hypertrophy, which is considered high-risk for Fabry's disease and forms the basis of screening studies. In screening studies in unexplained left ventricular hypertrophy individuals, the prevalence of Fabry disease varies between 0.4-12% (7-10). Kim WS et al. performed echocardiography in 988 male patients with left ventricular hypertrophy (≥ 13 mm), and Fabry disease prevalence was found to be 0.3% in the Korean population (7). Nakao et al. Echocardiography revealed in the Japanese population seven patients (3%) with Fabry disease in 230 male cohorts with left ventricular hypertrophy (≥ 13 mm). However, pathogenic mutation was identified in two of these patients (8). A cohort study was performed in 560 patients (362 males) with left ventricular hypertrophy in 10 centers in Belgium. Pathogenic GLA gene mutations were detected in two men (0.6%) and three women (1.7%), with a prevalence of 0.9% Fabry disease in patients with left ventricular hypertrophy (9). A study from Turkey unexplained left ventricular hypertrophy, in terms of 80 patients who Fabry disease, and screened by restriction enzyme analysis of gene mutations, in two cases (2.5%), Fabry disease has been identified (10). Niemann M et al. Performed standard echocardiography in 101 patients with concentric left ventricular hypertrophy (28 Fabry, 30

Friedreich, 34 isolated arterial hypertension, 9 amyloidosis) and 50 healthy controls. It was reported that papillary muscle mass was higher in Fabry patients compared to Friedreich and amyloidosis patients, and the ratio of papillary muscle size to left ventricular circumference was higher than hypertensive and amyloidosis patients. In addition, the ratio of papillary muscle size to the left ventricular circumference was increased in 22 of 28 Fabry patients (78%) (11). Combining these two parameters provides 75% sensitivity and 86% specificity to diagnose Fabry disease with left ventricular hypertrophy (11,12).

According to Fabry Outcome Survey (FOS) data published in 2009; the clinical findings and causes of death of 1453 patients (699 males, 754 females) from 19 countries worldwide were analyzed. The main causes of death of 181 Fabry patients (especially before 2001) were renal failure in men (42%) and cerebrovascular disease in women (25%). In contrast, cardiac involvement was the main cause of death in both male (34%) and female (57%) of 42 FOS-registered patients reported between 2001 and 2007 (13). According to the 2015 FOS data, the data of 740 Fabry patients who were followed and treated for approximately 5 years were examined. Findings from these retrospective comparisons of observational data and published literature support that enzyme replacement therapy slows the progression of renal failure and cardiomyopathy in the long term. It has also been reported that treatment delays the onset of morbidity and mortality (14). Especially in patients with cardiac involvement fabry disease, prognosis improves significantly with enzyme replacement therapy initiated especially at early stages (15). Therefore, in every adult patient with unexplained left ventricular hypertrophy, Fabry disease should be kept in mind. Early diagnosis is important in the prevention of cardiovascular and other system complications. Because of the multisystemic, variable and various clinical presentation of the disease, multidisciplinary follow-up is required.

CONCLUSION

In conclusion, echocardiography is a noninvasive and effective method in the diagnosis and follow-up of Fabry patients. Men, usually from the age of 30, and women, usually from the age of 40, most often present with unexplained left ventricular hypertrophy or hypertrophic cardiomyopathy without other proven aetiologies. They should be screened for Fabry disease, particularly when other findings (angiokeratoma, hypohidrosis, gastrointestinal abnormalities, corneal involvement) for Fabry disease are present, with subsequent careful interpretation of any variants identified in the GLA gene by a geneticist (16).

Competing interests: The authors declare that they have no competing interest.

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