Cardiac manifestations in patients with classical or cardiac subtype of Fabry disease

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Abstract

Background: Fabry disease (FD) is an X-linked lysosomal storage disorder engendered by a deficiency of the enzyme α-galactosidase A, leading to systemic accumulation of glycolipids. Studies have reported that the cardiac subtype of FD has a later onset and minimal extracardiac involvement. However, whether the severity of cardiac involvement differs between the classic and cardiac subtypes of FD remains unclear.

Methods: We enrolled consecutive patients with classic FD (n = 22; median age [25th–75th percentile], 47.0 [32.75–56.25] years; men, 72.7%) as well as age- and sex-matched patients with a later-onset cardiac subtype of FD who were selected from our cohort of patients with IVS4 919G>A mutation. FD was diagnosed on the basis of clinical symptoms/signs and pedigree screening of index case, plasma α-galactosidase activity, and molecular analysis. Data on clinical manifestations, laboratory findings, and echocardiogram findings were collected before enzyme replacement treatment. Disease severity was evaluated using the Mainz Severity Score Index score.

Results: All female patients demonstrated heterozygous mutations, with five, one, and four of them showing normal α-galactosidase activity, classic FD, and cardiac subtype of FD, respectively. The distributions of left ventricular performance indices and comorbidities, including hypertension, diabetes mellitus, and dyslipidemia, were similar between the two groups. Moreover, MSSI cardiovascular scores did not differ significantly between the groups (classic vs cardiac subtype, 10.0 [2.0–12.5] vs 10.5 [9.0–15.25]; $p = 0.277$).

Conclusion: Cardiac manifestations are similar between patients with classic and cardiac subtype of FD.

Keywords: Anderson–Fabry disease; Cardiac variant; Transthoracic echocardiography

1. INTRODUCTION

Fabry disease (FD), a genetic disease initially described in 1898, is an X-linked lysosomal storage disorder induced by a deficiency of the enzyme α-galactosidase A (α-GLA); a deficiency of α-GLA results in systemic accumulation of glycolipids, particularly globotriaosylsphingosine (Gb3), in multiple organs, including the cardiac, neural, and renal systems.[1,2] The estimated incidence of FD ranges from 1 in 40,000 to 1 in 117,000 worldwide.[3] Patients with classic FD show <1% α-galactosidase activity and typically present with symptoms such as neuropathic pain, cornea verticillata, and angiokeratoma right from their childhood or adolescence. Manifestations including hypertrophic cardiomyopathy, cardiac rhythm disturbance, progressive renal failure, and stroke constitute the long-term indications of FD.[4] In Taiwan, a high incidence of a cardiac subtype of FD with a special mutation (IVS4 919G>A) was discovered after newborn screening.[5] Its manifestations include concentric left ventricular hypertrophy (LVH), valvular involvement, and arrhythmias in the fifth to eighth decades of life, with minimal extracardiac involvement. However, the question as to whether the severity of cardiac involvement differs between these two types of FD remains unclear. Accordingly, we conducted this study to investigate this question by using echocardiographic findings, amino-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels, and the Mainz Severity Score Index (MSSI). MSSI is a clinical scoring system that is used to analyze the severity of FD and monitor its clinical course in response to enzyme replacement therapy (ERT).[6]

2. METHODS

We performed the study in accordance with the guidelines of the Declaration of Helsinki. The protocols were approved by an institutional review board and written informed consent was obtained from patients before participation.

We enrolled consecutive patients with classic FD (n = 22; median age, 47.0 [32.75–56.25] years; men, 72.7%); we also selected age- and sex-matched patients with the cardiac subtype of FD from our cohort of patients with the IVS4 + 919G>A mutation (n = 22; median age, 49.5 [33.75–57.0] years; men, 72.7%). FD was diagnosed on the basis of clinical symptoms/signs and pedigree screening of index case, plasma α-galactosidase activity, and molecular analysis of *GLA*. All female patients demonstrated heterozygous mutations, with five, one, and four of

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them showing normal range of α-galactosidase activity, classic FD, and cardiac subtype of FD, respectively.

We recorded data on clinical characteristics, including signs and symptoms, biochemical tests, and echocardiography findings, before the patients underwent ERT. Because the most common presentation, LVH, is usually symptomless initially, the disease duration is not precise, particularly in the cardiac subtype. Therefore, we used age-matched patients in this study to ensure the same duration of enzyme deficiency in both groups and thus minimize potential bias.

The MSSI cardiovascular score was used to assess disease severity. MSSI comprises four components that cover the general, neurological, cardiovascular, and renal signs and symptoms of FD. Different specialists, including a dermatologist, neurologist, ophthalmologist, and cardiologist, recorded a detailed medical history of and performed clinical investigations on the patients. The maximum MSSI score for the general and renal components is 18, and that for the neurological and cardiovascular components is 20. The sum of the scores for these individual components constitutes the total MSSI score. The severity of FD can be divided into three categories according to the total MSSI score: mild, <20; moderate, 20–40; and severe, >40.[6]

According to the recommendations of the American Society of Echocardiography, we measured left ventricular parameters, including left ventricular mass (LVM), diastolic interventricular septal thickness, systolic and diastolic left ventricular internal diameter, and diastolic left ventricular posterior wall thickness, by using serial two-dimensional guided M-mode echocardiography.[7,8] LVM was calculated using the American Society of Echocardiography simplified cubed equation.

All results are reported as median (25th–75th percentile) and numbers (%). Variables were compared using the Wilcoxon rank-sum test or Pearson's χ^2 test, as appropriate. Statistical analyses were performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

3. RESULTS

Table 1 presents the baseline characteristics of the patients in the two groups. The patients were adequately matched for age and sex. Comorbidities, including hypertension, diabetes mellitus, and dyslipidemia, showed similar distributions between the classic FD and cardiac subtype groups; however, the frequency of smoking was higher in the cardiac subtype group (classic type vs cardiac subtype: 4.5% vs 18.2%; $p = 0.039$). Moreover, blood pressure levels were similar between the two groups; nevertheless, the resting heart rate was higher in the cardiac subtype group (classic type vs cardiac subtype: median, 59.6 [25th–75th percentile: 55.8–62.6] vs 64.9 [25th–75th percentile: 58.7–75.2]; $p = 0.025$). No significant differences existed between the two groups in terms of renal function parameters, lipid profile, or NT-pro-BNP levels. Table 2 lists cardiac structure and function indices investigated using echocardiography, including the left ventricular dimension in the end diastolic and systolic phases, left ventricular septal and posterior wall thickness, ejection fraction, LVM, left atrial dimension, pulmonary arterial systolic pressure, and tricuspid annular plane systolic excursion; we noted that these indices were comparable between the two groups. One patient in each group underwent permanent pacemaker implantation.

The total MSSI score was significantly higher for the classic FD group compared with the cardiac subtype group. This was because the classic FD group had higher scores for the general (classic type vs cardiac subtype; median, 1.0 [25th–75th percentile: 0.0–3.0] vs 0.0 [25th–75th percentile: 0.0–1.0]; $p = 0.001$), neurological (classic type vs cardiac subtype: median, 5.0 [25th–75th percentile: 0.0–6.0] vs 0.0 [25th–75th percentile: 0.0–1.5]; $p = 0.002$), and renal (classic type vs cardiac subtype: median, 4.0 [25th–75th percentile: 0.0–4.0] vs 0.0 [25th–75th percentile: 0.0–0.0]; $p = 0.007$) components. The scores for the cardiovascular component did not differ significantly between

Table 1

Baseline characteristics of patients with classical type vs cardiac subtype

Demographic data	Classical subjects N = 22 N (%)	Cardiac subjects N = 22 N (%)	*p*
Age (y)	47.0 (32.75–56.25)	49.5 (33.75–57.0)	0.655
Gender			
Male	16 (72.7)	16 (72.7)	1.000
Female	6 (27.3)	6 (27.3)	
Laboratory data			
Systolic BP (mmHg)	114.0 (105.5–128.25)	120.5 (106.0–146.75)	0.291
Diastolic BP (mmHg)	68.5 (64.125–71.625)	74.5 (63.5–86.0)	0.093
Heart rate	59.6 (55.8–62.6)	64.9 (58.7–75.2)	0.025
Blood urea nitrogen	12.0 (11.0–16.25)	15.0 (13.0–16.0)	0.247
Creatinine	0.81 (0.65–0.9475)	0.81 (0.68–0.98)	0.979
eGFR (mL/min/1.73 m^2)	83.6 (59.8–112.2)	86.1 (66.4–102.3)	0.937
Cholesterol (mg/dL)	184.0 (140.0–244.0)	187.0 (155.5–198.0)	0.490
Triglyceride (mg/dL)	79 (53.0–152.0)	127.5 (74.25–226.0)	0.117
HDL-cholesterol (mg/dL)	55.5 (52.75–59.0)	50.0 (44.5–60.5)	0.163
LDL-cholesterol (mg/dl)	113.5 (82.0–149.5)	104.0 (88.5–127.0)	0.546
NT-proBNP (pg/mL)	145.8 (24.71–1341)	42.7 (19.2–156.4)	0.316
Comorbidities			
Hypertension	9 (40.9)	10 (45.5)	0.223
Diabetes mellitus	1 (4.5)	2 (9.1)	0.554
Dyslipidemia	5 (22.7)	1 (4.5)	0.082
Smoking	1 (4.5)	4 (18.2)	0.039

The data were presented as median (25th percentile–75th percentile).
BP = blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro-Brain Natriuretic Peptide.

Table 2

Echocardiographic findings of patients with classical type vs cardiac subtype

Demographic data	Classical subjects N = 22	Cardiac subjects N = 22	*p*
Echocardiographic findings			
Aortic root (mm)	26.5 (26.0–30.0)	29.0 (26.0–30.25)	0.171
IVSTd (mm)	11.0 (9.0–14.0)	10.0 (8.0–13.25)	0.645
PWTd (mm)	11.5 (10.0–13.0)	10.5 (8.0–13.75)	0.554
LVIDd (mm)	45.0 (41.0–49.25)	45.5 (41.25–50.25)	0.503
LVIDs (mm)	26.0 (23.0–32.0)	27.5 (25.0–32.0)	0.823
LVEDV (mL)	90.0 (74.0–116.0)	96.0 (77.5–120.0)	0.883
LVESV (mL)	25.0 (18.0–44.0)	30.0 (22.5–39.0)	0.376
LVEF (%)	70.0 (66.75–75.25)	68.0 (60.5–73.8)	0.496
LV mass (g)	191.5 (130.5–246.75)	154.0 (121.5–225.0)	0.882
LV mass index (g/m^2)	115.8 (81.5–138.5)	90.1 (66.9–133.9)	0.918
Left atrium (mm)	34.0 (30.75–36.5)	32.8 (27.0–36.5)	0.417
PASP (mmHg)	24.0 (21.0–29.0)	22.0 (13.0–25.0)	0.053
TAPSE (mm)	2.0 (2.0–3.0)	2.0 (2.0–2.0)	0.221

IVSTd = interventricular septum thickness in end-diastole; PWTd = posterior wall thickness in end-diastole; LVIDd = left ventricular internal dimension in end-diastole; LVIDs = left ventricular internal dimension in end-systole; LVEDV = left ventricular end-diastole volume; LVESV = left ventricular end-systole volume; LVEF = left ventricular ejection fraction; PASP = pulmonary arterial systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

Table 3

Mainz Severity Score Index of patients with classical type vs cardiac subtype

Demographic data	Classical subjects N = 22	Cardiac subjects N = 22	*p*
General score	1.0 (0.0–3.0)	0.0 (0.0–1.0)	0.001
Characteristic facial	0 (0)	0 (0)	1.000
Angiokeratoma	2 (9.1)	0 (0)	0.148
Edema	2 (9.1)	0 (0)	0.148
Musculoskeletal	4 (18.2)	0 (0)	0.036
Cornea verticillata	7 (31.8)	0 (0)	0.004
Diaphoresis			0.060
Hypo/hyperhidrosis	1 (4.5)	0 (0)	
Anhidrosis	4 (18.2)	0 (0)	
Abdominal pain	1 (4.5)	0 (0)	0.312
Diarrhea/constipation	1 (4.5)	0 (0)	0.312
Hemorrhoids	0 (0)	0 (0)	1.000
Pulmonary	2 (9.1)	1 (4.5)	0.550
NYHA			0.769
Class I	4 (18.2)	6 (27.3)	
Class II	1 (4.5)	1 (4.5)	
Class III	0 (0)	0 (0)	
Class IV	0 (0)	0 (0)	
Appearance			
Neurologic score	5.0 (0.0–6.0)	0.0 (0.0–1.5)	0.002
Tinnitus	0 (0)	1 (4.5)	0.312
Vertigo	2 (9.1)	1 (4.5)	0.550
Acroparesthesia			
Occasional	6 (27.3)	3 (13.6)	<0.001
Chronic	9 (40.9)	0 (0)	
Fever pain crisis	4 (18.2)	0 (0)	0.036
Cerebrovascular	0 (0)	2 (9.1)	0.148
Psychiatric			
Depression	0 (0)	0 (0)	1.000
Fatigue	1 (4.5)	1 (4.5)	1.000
Reduced activity level	0 (0)	2 (9.1)	0.148
Cardiovascular score	10.0 (2.0–12.5)	10.5 (9.0–15.25)	0.277
Left ventricle hypertrophy			
Thickening of wall	1 (4.5)	0 (0)	0.197
LVH seen in ECG	3 (13.6)	0 (0)	
Cardiomyopathy (<15 mm)	9 (40.9)	11 (50)	
Severe cardiomyopathy (>15 mm)	4 (18.2)	8 (36.4)	
ECG abnormalities	13 (59.1)	11 (50)	0.545
Hypertension	9 (40.9)	13 (59.1)	0.228
Valve insufficiency	20 (90.9)	19 (86.4)	0.635
Pacemaker	1 (4.5)	1 (4.5)	1.000
Renal score	4.0 (0.0–4.0)	0.0 (0.0–0.0)	0.007
Proteinuria	10 (45.5)	3 (13.6)	0.021
Low GFR	2 (9.1)	1 (4.5)	0.550
Creatinine > 3.5 mg/dL	0 (0)	0 (0)	1.000
Dialysis	1 (4.5)	0 (0)	0.312
Total score	17.5 (13.25–23.0)	14.5 (9.75–18.0)	0.051

We expressed the individual parameter with number (percentage) for categorical variables and median (25th percentile–75th percentile) for numerical variables.
GFR = glomerular filtration rate; LVH = left ventricular hypertrophy.

the two groups (classic type vs cardiac subtype: median, 10.0 [25th–75th percentile: 2.0–12.5] vs 10.5 [25th–75th percentile: 9.0–15.25]; $p = 0.277$; Table 3 and Figure 1).

Regarding the general component, the classic FD group exhibited a higher prevalence of cornea verticillata (classic type vs cardiac subtype, 7 [31.8] vs 0 [0]; $p = 0.004$) and musculoskeletal disorders (classic type vs cardiac subtype, 4 [18.2] vs 0 [0]; $p = 0.036$). Furthermore, concerning the neurological component, the classic FD group had a higher prevalence of acroparesthesia (classic type vs cardiac subtype, 15 [68.2] vs 3 [13.6]; $p < 0.001$) and fever/pain crisis (classic type vs cardiac subtype, 4 [18.2] vs 0 [0]; $p = 0.036$). Regarding the renal component, the classic FD group exhibited more severe proteinuria (classic type vs cardiac subtype, 10 [45.5] vs 3 [13.6]; $p = 0.021$).

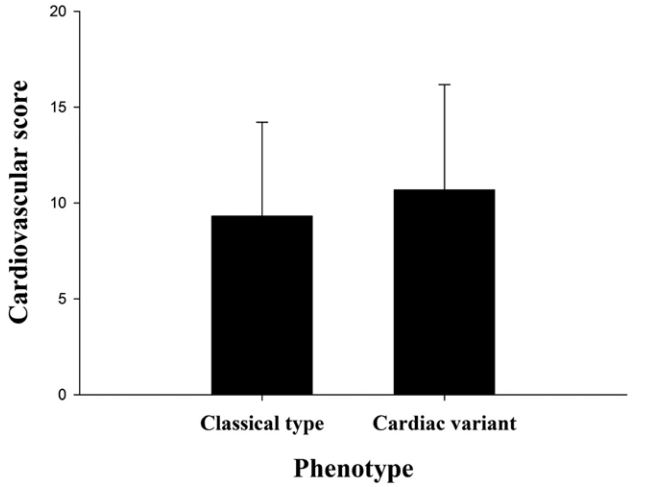

Fig. 1 Cardiovascular subscore of the Mainz Severity Score Index (MSSI) in patients with classic and cardiac subtypes of Fabry disease. The error bars represent standard deviation.

4. DISCUSSION

Our study's most noteworthy finding is that cardiovascular manifestations were similar between the classic and cardiac subtype of FD according to echocardiographic findings, NT-proBNP levels, and MSSI scores.

FD is an X-linked lysosomal storage disorder resulting from a deficiency of the enzyme α-GLA, which leads to a systemic accumulation of glycolipids in major organs, particularly in the vascular endothelium and smooth muscle cells of the renal and cardiovascular systems.[9,10] Classic symptoms observed in hemizygous male patients include acroparesthesia, angiokeratoma, hypohidrosis, corneal opacities, and dysfunction of the kidney, brain, and heart. The cardiac manifestations of FD include LVH,[11] valvular involvement,[12] and arrhythmias,[13] which usually present in the fifth to eighth decades of life. Atypical variants of FD that occur because of residual low levels of α-GLA activity, resulting in a "milder" and later-onset phenotype,[14] are being increasingly recognized. We demonstrated that the degrees of severity of cardiac manifestations were similar between the classic FD and cardiac subtype groups, as indicated by echocardiographic findings and MSSI scores. A previous study revealed that the MSSI score is a highly specific tool for distinguishing FD from other severe afflictions and that it could be used to evaluate disease severity.[6] The severity of FD (MSSI) is significantly correlated with age.[15,16]

The increasing frequency of later-onset mutations detected through neonatal screening may render FD a broad cardiovascular problem that extends beyond childhood. In general, cardiac manifestations of FD, such as arrhythmia, angina, and LVH, are considered to result from Gb3 accumulation in the sinoatrial node, conduction system, vascular endothelium, and cardiomyocytes. Moreover, the more severe the α-Gal A defect is, the more severe the clinical manifestations are and the earlier the disease onset becomes. Our findings suggest that Gb3 accumulation is

not the only factor determining the clinical symptoms of FD.[17] A previous study revealed that glycolipid accumulation in the myocardium constitutes only 1%–3% of the total mass in a hypertrophic heart.[18] Other pathogenic factors such as inflammatory cytokines[19–22]and oxidative stress may also contribute to clinical manifestations.[19,23–25]

With the availability of ERT as a possible treatment, cardiac disease has become the leading cause of death in patients with FD.[26,27] Improvement in renal care and early initiation of ERT can reduce the impact of renal disease as a cause of death in patients with FD.[28,29] Previous research reported that early ERT also led to favorable outcomes in patients with Fabry cardiomyopathy.[30] Moreover, a study indicated that late diagnosis was a factor for early death in patients with FD.[27] Although the level of cardiac involvement in the cardiac subtype of FD is similar to that in classic FD, the cardiac subtype of FD is usually diagnosed late because of minimal extracardiac involvement.[31] Therefore, early diagnosis, careful evaluation of disease progression, and early initiation of therapy might be crucial to improve the outcomes of patients with FD of the cardiac subtype.

This study has some limitations. First, our sample size was small because of the limited number of patients with classic FD. The rare nature of the disease contributed to the small sample size, although we included all consecutive cases of classic FD. Second, classic FD is usually diagnosed early because of extracardiac manifestations. However, we chose age- and sex-matched patients with cardiac subtype of FD to reduce potential confounding factors.

In conclusion, our results demonstrate no significant differences between the classic and cardiac subtypes of FD in terms of echocardiographic findings or MSSI cardiovascular scores. Therefore, we suggest that the levels of severity of cardiac involvement are similar in both subtypes of FD. These findings should be considered in the clinical evaluation and treatment of FD.

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