JACC Vol 7, No 5
May 1986:1157–61

Echocardiographic Abnormalities and Disease Severity in Fabry's Disease

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Fabry's disease is an X-linked recessive genetic deficiency of the enzyme alpha-galactosidase A, which leads to the pathologic deposition of neutral glycosphingolipids in lysosomes of the vascular endothelium of the heart, brain and kidney. The disease is progressive in hemizygous male patients, with increasing involvement of the major organs leading to death. Because cardiac involvement is a constant feature, echocardiograms were performed on 35 patients with Fabry's disease, 23 hemizygotes (aged 28.6 ± 14 years) and 12 heterozygotes (aged 31.6 ± 6 years), to determine whether cardiac involvement could be detected noninvasively.

The results demonstrated that hemizygous male patients had a greater aortic root diameter, thicker interventricular septum and greater ventricular mass than did heterozygous female patients. Left ventricular mass per square meter of body surface area correlated well with clinical disease severity ($r = 0.68$, $p < 0.05$), suggesting progressive glycosphingolipid deposition. Older heterozygotes (>25 years old) had more severe evidence of cardiac disease than did younger male patients. Although mitral valve prolapse was identified in 12 (54%) of 23 male hemizygotes and in 7 (58%) of 12 female heterozygotes, its presence did not correlate with clinical disease severity or other echocardiographic variables. Therefore, echocardiographic evidence of Fabry's disease appears to correlate with age-related disease severity and may be a useful noninvasive marker to follow disease progression and possible regression when appropriate therapy becomes available.

(J Am Coll Cardiol 1986;7:1157–61)

Fabry's disease is an X-linked recessive inborn error of glycosphingolipid metabolism. The deficient activity of the enzyme alpha-galactosidase A results in the accumulation of a neutral glycosphingolipid, globotriaosylceramide, primarily in the vascular endothelial lysosomes as well as in lysosomes of the kidneys, cardiac muscle and heart valves (1,2). The disease is progressive, with symptoms becoming more severe with increasing age in hemizygous male patients, whereas heterozygous female patients are usually asymptomatic or have only mild manifestations of the disease. Although cardiac involvement is not always clinically apparent, it is a constant pathologic feature (3). Glycosphingolipid deposition occurs in the cardiac conduction system, myocardium, aorta and valve leaflets resulting in conduction abnormalities, congestive, restrictive or hypertrophic cardiomyopathy, degeneration of the walls of the ascending aorta and mitral insufficiency (4–6). Progressive vascular disease of the heart, kidney or central nervous system, which is the usual cause of death, occurs in the third to fifth decades of life.

In this study we attempted to determine whether cardiac abnormalities in Fabry's disease, especially of the mitral valve, can be detected echocardiographically and whether they correlate with disease severity or progression of disease with age, or both.

Methods

Study patients. Thirty-five patients with Fabry's disease were studied: 23 male hemizygotes (aged 28.6 ± 14 years) and 12 female heterozygotes (aged 31.4 ± 6 years). Three additional patients, one heterozygote with concomitant hypertrophic cardiomyopathy and two hemizygotes with blood pressure greater than 140/90 mm Hg, were excluded. Each patient underwent clinical evaluation (including car-

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Manuscript received June 11, 1985; revised manuscript received December 18, 1985, accepted December 30, 1985.

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0735-1097/86/$3 50

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Table 1. Comparison of Echocardiographic Variables Between Hemizygous Male and Heterozygous Female Patients With Fabry's Disease

	Hemizygous Males	Heterozygous Females	p Value
No. of patients	23	12	
Age (yr)	28.6 ± 14	31.4 ± 6.2	NS
LA (cm/m^2)	1.9 ± 0.3	1.9 ± 0.4	NS
AO (cm/m^2)	2.1 ± 0.3	1.7 ± 0.2	<0.001
IVS (mm)	11.1 ± 3.0	8.8 ± 1.0	<0.02
LVPW (mm)	10.9 ± 2.9	9.2 ± 1.3	<0.06
EDD (mm)	45.4 ± 6.7	44.6 ± 5.2	NS
ESD (mm)	29.2 ± 6.3	29.3 ± 4.6	NS
FS	0.36 ± 0.07	0.34 ± 0.06	NS
Mass/BSA (g/m^2)	122.3 ± 42.6	86.1 ± 14.3	<0.01

All data are expressed as mean ± SD. AO = aortic diameter; EDD = end-diastolic dimension; ESD = end-systolic dimension; FS = fractional shortening; IVS = interventricular septal thickness; LA = left atrial diameter; LVPW = left ventricular posterior wall thickness; Mass/BSA = mass divided by body surface area; NS = not significant.

diac auscultation by a cardiologist) and electrocardiographic, echocardiographic and laboratory examinations. Each hemizygote had typical clinical manifestations of Fabry's disease, essentially no detectable levels of alpha-galactosidase A activity in plasma, isolated leukocytes and cultured skin fibroblasts and elevated urinary and plasma globotriaosylceramide levels. Heterozygous female patients had intermediate levels of alpha-galactosidase A activity.

Echocardiography. Echocardiograms were performed in the supine position using either an ATL Mark 6000 two-dimensional mechanical sector scanner or an Irex ContinuTrace M-mode system. Two-dimensional guidance was utilized to obtain optimal M-mode beam orientation in all but five patients who were studied before the introduction of two-dimensional echocardiography in this institution. Measurements were made using the leading edge method in accordance with the recommendations of the American Society of Echocardiography (7). Fractional shortening was calculated by dividing the difference between the end-diastolic dimension and the end-systolic dimension by the end-diastolic dimension. Left ventricular (LV) mass was calculated from the M-mode echocardiogram using the formulas (8,9):

$$\text{LV mass}_{\text{echo}} = (\text{LVID} + 2\text{MMT}^3) - \text{LVID}^3$$

and

$$\text{LV mass}_{\text{actual}} = 0.7\ \text{LV mass}_{\text{echo}} + 2.4\ \text{g},$$

where LVID is the left ventricular internal dimension and MMT is the mean myocardial thickness (the sum of left ventricular posterior wall and septal thickness divided by 2).

The mitral valve was examined for abnormal echocardiographic patterns. Because they are well-established, M-mode criteria were used as the standard to define the presence of mitral prolapse. Mitral valve prolapse was defined as either 1) late systolic posterior motion of one or both leaflets, or 2) holosystolic hammocking with the maximal posterior excursion of one leaflet at least 3 mm below the C-D line, or both. A redundant mitral valve was defined as more than three parallel systolic mitral echoes. Physiologic

Table 2. Comparison of Echocardiographic Variables Between Male Hemizygotes With Fabry's Disease Younger and Older Than 25 Years

		Fabry's Disease		
	Normal Adults	>25 yr	<25 yr	p Value
No. of subjects	14	8	15	—
AO (cm/m^2)	2.0 to 3.7	2.2 ± 0.3	2.0 ± 0.3	NS
LA (cm/m^2)	1.9 to 4.0	1.9 ± 20	1.9 ± 0.4	NS
IVS (mm)	6 to 11	9 ± 1.8	12.2 ± 3.0	<0.02
LVPW (mm)	6 to 11	8.4 ± 1.8	12.3 ± 2.3	<0.001
Mass/BSA (g/m^2)		94.6 ± 18.6	138.1 ± 44.7	<0.02
Age (yr)		12 ± 3.7	37 ± 8	<0.001
State		1.9 ± 1.6	3.13 ± 1.5	<0.02
Gal		0.33 ± 0.15	0.31 ± 0.2	NS

Gal = activity of enzyme alpha-galactosidase A; State = clinical state based on evidence of disease, as discussed in text; other abbreviations as in Table 1.

maneuvers were not routinely used to evoke prolapse. All echocardiograms were read blindly by three reviewers, with the consensus opinion taken. Interobserver agreement was greater than 95%. Echocardiograms were performed as part of a series of screening tests before confirmation of the presence or absence of Fabry's disease and were interpreted without knowledge of the other test results.

Control group. The results from the patients with Fabry's disease were then compared with data in an age-matched control group consisting of 40 men 25 to 44 years old: 20 with mitral valve prolapse and 20 normal volunteers. There were no other echocardiographic differences between these two groups. The findings from our female patients were compared with a similarly composed age-matched normal control group.

Classification of disease severity. A disease severity scale (0 to 4+) was established (by R.J.D.) based on the extent of clinical end-organ involvement, that is, severity of renal, cardiac and cerebrovascular manifestations, and applied without knowledge of the results of the echocardiogram. The scale was interpreted as follows: 0 = asymptomatic; 1 = mild, occasional acroparesthesia and angiokeratoma only; 2 = mild to moderate clinically symptomatic; 3 = mild to moderate clinically symptomatic renal, cardiac or cerebrovascular involvement, or both, without clinical disability; 4 = clinically significant disease, namely, renal changes on computed axial tomography or ultrasound, or clinical renal disease; 5 = severe clinical disease, end-stage renal disease.

Statistical analysis. Quantitative differences between the different subgroups were evaluated by Student's *t* tests; qualitative differences were evaluated by the chi-square statistic. The hypotheses that two variables were significantly correlated were tested by least-squares linear regression analysis. Group data are expressed as mean ± SD. Differences between patient and control groups were tested by the *t* test for independent variables.

Results

Echocardiographic findings. There were distinct echocardiographic differences between clinically affected hemizygous male patients and the clinically asymptomatic heterozygous female patients (Table 1). Male hemizygotes had a significantly greater aortic root diameter corrected for body surface area (2.07 ± 0.3 versus 1.69 ± 0.2 cm/m^2, $p < 0.001$), thicker interventricular septum (11.1 ± 3 versus 8.8 ± 1 mm, $p < 0.02$) and greater left ventricular mass/body surface area (122.2 ± 43 versus 86.1 ± 14 g/m^2, $p < 0.01$) than female heterozygotes. Hemizygotes were similar to heterozygotes with regard to left atrial size (1.92 ± 0.3 versus 1.92 ± 0.4 mm/m^2, p = NS), left ventricular posterior wall thickness (10.9 ± 0.3 versus 9.2 ± 1 mm, p = 0.06), left ventricular end-diastolic dimension (45.4 ± 7 versus 44.6 ± 5 mm, p = NS), systolic dimension (29.2 ± 6 versus 29.3 ± 5 mm, p = NS) and fractional shortening (0.36 ± 0.07 versus 0.34 ± 0.06, p = NS).

Left ventricular mass. Importantly, left ventricular mass per square meter correlated well with clinical disease severity in all hemizygotes ($r = 0.68$, $p < 0.05$). Because Fabry disease progresses with age, the male patients were arbitrarily classified into two groups: those older and those younger than 25 years (Table 2). The older male hemizygotes had a thicker interventricular septum (12.2 ± 3 versus 9.0 ± 1.8 mm, $p < 0.02$), left ventricular posterior wall (12.3 ± 2.3 versus 8.4 ± 1.8 mm, $p < 0.001$) and mass/body surface area (138.1 ± 45 versus 94.6 ± 19 g/m^2, $p < 0.02$). To exclude the possibility that the increased wall thickness was age related, hemizygotes older than 25 years old (15 patients; mean age 37 ± 8 years, range 29 to 48) were compared with an age-matched control group: interventricular septum was thicker in hemizygote patients ($p < 0.001$), as was left atrial size ($p < 0.01$), left ventricular posterior wall thickness ($p < 0.001$) and aortic root size ($p < 0.001$). Myocardial ultrasound reflectance was not altered, as has been reported in another infiltrative disease, amyloidosis (8). As expected, female heterozygotes did not differ from the control group in any of the measured echocardiographic variables.

Mitral valve abnormalities. Mitral valve prolapse was identified in 12 (52%) of the 23 male hemizygotes and in 7 (58%) of the 12 female heterozygotes. Cardiac auscultation (specifically the presence of a mitral click) correlated well with echocardiographic findings of mitral valve prolapse. A redundant mitral valve was seen in 14 of the remaining 16 patients: 10 of 11 hemizygotes and 4 of 5 heterozygotes. A totally normal mitral valve was seen in only one patient, a female heterozygote. There was no correlation between the presence or absence of mitral valve abnormalities and the clinical severity of Fabry's disease. There was no correlation between the mitral valve abnormalities and other echocardiographic variables for either hemizygotes or heterozygotes.

Electrocardiography. Routine electrocardiography was less accurate than echocardiography in detecting abnormalities. In male hemizygotes, electrocardiography had a sensitivity of only 0.64 and a specificity of 0.88 for the detection of left ventricular hypertrophy. Additionally, two patients with mild concentric hypertrophy had an electrocardiographic pattern of an inferior wall myocardial infarction.

Discussion

Mitral valve involvement. Cardiac involvement is a major morbid manifestation of Fabry's disease (1–6). Pathologically, the mitral valve is the most common valve involved. Desnick et al. (2) reported pathologic evidence of inter-

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chordal hooding with thickening of the mitral valve leaflets and papillary muscles. Ultrastructural examination of the cardiac valves revealed electron-dense inclusion bodies in lysosomes consistent with biochemical analyses which revealed markedly increased concentrations of globotriaosylceramide in the mitral valve.

Several other genetic diseases have also been associated with mitral valve prolapse. These include Marfan's syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, Duchenne's muscular dystrophy, Turner's syndrome, Noonan's syndrome, osteogenesis imperfecta and myotonic dystrophy. Other lysosomal storage diseases have mitral valve involvement including mucopolysaccharidosis types I and II, G_{M1} gangliosidosis type 1 and G_{M2} gangliosidosis type 2. In addition, mitral valve prolapse has been associated with connective tissue abnormalities, coagulopathies and thoracoskeletal disorders (10–12).

The high prevalence of echocardiographically documented mitral valve prolapse and redundancy in Fabry's disease has not been previously appreciated. In the present study of 35 patients, 54% had mitral valve prolapse. The incidence of mitral valve abnormalities was similar in both hemizygotes and heterozygotes. Importantly, there was no correlation between disease severity, age or other echocardiographic variables and the presence or absence of mitral valve abnormalities. The echocardiographic mitral valve abnormalities may be a marker of glycosphingolipid deposition, creating a thicker but mobile valve with a tendency to prolapse into the left atrium. Because maneuvers were not performed routinely, the propensity for the redundant valves to prolapse could not be determined. In the single previous echocardiographic study (13), only 1 of 32 patients with Fabry's disease was reported to have an abnormal mitral valve. However, in that study, only a dedicated M-mode machine was utilized, emphasis was placed on chamber dimensions and mitral valve imaging was not pursued when the study was technically difficult. In the present study, both M-mode and two-dimensional equipment were used, thereby improving the ability to fully image the mitral valve even in difficult cases.

Ventricular abnormalities. Another significant echocardiographic feature of Fabry's disease was the increased left ventricular wall thickness and greater ventricular mass with increasing age and disease severity in hemizygotes. Bass et al. (13) also found that the majority of hemizygotes studied pathologically had increased wall thickness, which probably represents progressive glycosphingolipid deposition in the myocardium. It is unlikely that mitral valve prolapse alone could account for these changes, because the mitral prolapse in this study was not associated with clinically significant mitral regurgitation. Therefore, left ventricular wall thickness and mass, readily obtainable by echocardiography, may be a noninvasive marker to estimate clinical Fabry's disease severity, and may be used to follow disease progression and possible regression in response to therapeutic interventions. However, sequential echocardiographic studies, and potentially, endomyocardial biopsies will be necessary to document the rate of progression of ventricular mass and wall thickness to determine how closely they correlate with overall disease severity, and whether the cardiac abnormalities may predict the clinical course. Interestingly, as documented in other disease states, the electrocardiogram was not as helpful as the echocardiogram in detecting left ventricular hypertrophy (14).

Conclusions. Patients with Fabry's disease have a high incidence of mitral valve abnormalities as detected by echocardiography. In addition, left ventricular wall thickness and mass appear to correlate with the severity of their disease. It is therefore recommended that patients with Fabry's disease undergo careful auscultation and echocardiographic examination to evaluate the presence of mitral valve abnormalities and increased wall thickness. These findings may serve as noninvasive markers of the disease when therapeutic interventions are available.

References

1. Desnick RJ, Sweeley CC. Fabry disease: deficient alpha-galactosidase A activity. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS, eds. The Metabolic Basis of Inheritable Disease. New York:McGraw-Hill, 1983:906–44.
2. Desnick RJ, Bleiden LC, Sharp HL, Hofschire PJ, Moller JH. Cardiac valvular anomalies in Fabry's disease: clinical morphologic and biochemical studies. Circulation 1976;54:818–24.
3. Ferrans VJ, Hibbs RB, Burda CD. The heart in Fabry's disease: a histochemical and electron microscopic study. Am J Cardiol 1969;24: 95–110.
4. Mossard JM, Jessot G, Wolfe LS, Batzenschtager A, Stoebner P, Metzger H. The heart in Fabry's disease. Arch Mal Coeur 1972;65: 495–500.
5. Becker NE, Schoorl R, Balk AG, van der Heide RM. Cardiac manifestations of Fabry's disease: report of a case with mitral insufficiency and electrocardiographic evidence of myocardial infarction. Am J Cardiol 1975;36:829–35.
6. Colucci WS, Lorell Bh, Schoer FJ, Warhol MJ, Grossman W Hypertrophic obstructive cardiomyopathy due to Fabry's disease. N Engl J Med 1982;307:926–8.
7. Sahn DJ, DeMaria A, Kiss J, Weyman A. The Committee for M-mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072–8.
8. Woythaler JN, Singer SL, Kwan OL, et al. Accuracy of echocardiography in detecting left ventricular hypertrophy: comparison with postmortem mass measurements. J Am Coll Cardiol 1983;2:305–11.
9 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1977;55:613–8.
10. Lebwohl MG, Distefano D, Prioleau PG, Uram M, Yannuzzi LA, Fleischmajer R. Pseudoxanthoma elasticum and mitral valve prolapse: linked mesenchymal dysplasias. N Engl J Med 1982;307:228–31.
11. Pickering NJ, Brody JI, Barrett MJ. Von Willebrand syndromes and

mitral valve prolapse: linked mesenchymal dysplasias. N Engl J Med 1981;305:131–4.

12. Schutte JE, Gaffney FA, Blend L, Blongvist CG. Distinctive anthropomorphic characteristics of women with mitral valve prolapse. Am J Med 1981;71:533–8.

13. Bass JL, Shrivastava S, Grabowski GA, Desnick RJ, Moller JH. The M-mode echocardiogram in Fabry's disease. Am Heart J 1980;100: 807–12.

14. Murphy M, Thenabadu PN, Soyza N, Meade J, Doherty JE, Baker BJ. Sensitivity of electrocardiographic criteria for left ventricular hypertrophy according to type of cardiac disease. Am J Cardiol 1985;55:545–9.