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Prevalence of Anderson-Fabry Disease in Male Patients With Late Onset Hypertrophic Cardiomyopathy

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Background—Although studies have suggested that "late-onset" hypertrophic cardiomyopathy (HCM) may be caused by sarcomeric protein gene mutations, the cause of HCM in the majority of patients is unknown. This study determined the prevalence of a potentially treatable cause of hypertrophy, Anderson-Fabry disease, in a HCM referral population.

Methods and Results—Plasma α-galactosidase A (α-Gal) was measured in 79 men with HCM who were diagnosed at $\geq$40 years of age (52.9$\pm$7.7 years; range, 40–71 years) and in 74 men who were diagnosed at $<$40 years (25.9$\pm$9.2 years; range, 8–39 years). Five patients (6.3%) with late-onset disease and 1 patient (1.4%) diagnosed at $<$40 years had low α-Gal activity. Of these 6 patients, 3 had angina, 4 were in New York Heart Association class 2, 5 had palpitations, and 2 had a history of syncope. Hypertrophy was concentric in 5 patients and asymmetric in 1 patient. One patient had left ventricular outflow tract obstruction. All patients with low α-Gal activity had α-Gal gene mutations.

Conclusion—Anderson-Fabry disease should be considered in all cases of unexplained hypertrophy. Its recognition is important given the advent of specific replacement enzyme therapy. ***(Circulation. 2002;105:1407-1411.)***

Key Words: Anderson-Fabry disease ■ cardiomyopathy ■ hypertrophy

Hypertrophic cardiomyopathy (HCM) is defined by the presence of unexplained myocardial hypertrophy. In the majority of patients, the disease is caused by autosomal-dominant inherited mutations in 1 of 9 genes that encode different cardiac sarcomeric proteins.[1] In 1995, Nakao and colleagues[2] reported a 3% prevalence of Anderson-Fabry disease in predominantly middle-aged male patients with left ventricular hypertrophy (LVH) associated with diverse pathologies. The implication of their study was that this now-treatable disease is frequently undiagnosed. The aim of the present study was to determine the prevalence of Anderson-Fabry disease in a referral population of male patients with a clinical diagnosis of HCM.

Methods

Patients

The study cohort was composed of 79 consecutive men with HCM who were first diagnosed at $\geq$40 years of age (mean, 52.9$\pm$7.7 years; range, 40 to 71 years). A total of 74 men diagnosed at $<$40 years of age (mean, 25.9$\pm$9.2 years; range, 8 to 39 years) were studied for comparison. All had apparently unexplained LVH with a maximum left ventricular wall thickness $\geq$13 mm. Clinical examination, supine 12-lead electrocardiography, and ambulatory 48-hour ECG monitoring were performed in all patients.

M-mode, 2D, and Doppler echocardiography were performed as previously described[3] using a GE System V echocardiograph. The severity and distribution of LVH were assessed in the parasternal short-axis plane at the mitral valve and papillary muscle level. Maximum left ventricular wall thickness was defined as the greatest thickness in any single segment. Patterns of hypertrophy were defined in accordance with previously published methods.[3] Maximal left ventricular outflow tract flow velocity was determined using continuous-wave Doppler, and pressure gradients were calculated using the simplified Bernoulli equation. Left ventricular inflow velocities were obtained from the apical 4-chamber view using pulsed-wave Doppler echocardiography.

Screening for Anderson-Fabry Disease

Plasma α-galactosidase A (α-Gal) activity was measured with the fluorogenic substrate 4-methylumbelliferyl-α-D-galactopyranoside (Sigma), with N-acetyl-D-galactosamine (Nacalai Tesque) used as an inhibitor of α-N-acetylgalactosaminidase as described previously.[2] On the basis of previously published data, a plasma α-Gal activity of <1.2 nmol $\cdot$ h^{-1} $\cdot$ mL^{-1} was considered diagnostic of Anderson-Fabry disease.[2] Plasma α-Gal activity in 89 normal healthy men (aged 52$\pm$19 years; range, 14 to 80 years) was also measured.

Genetic Analysis

Mutations in the α-Gal gene were identified by amplifying each exon using polymerase chain reaction, followed by single-strand conformation polymorphism analysis (SSCP) and direct sequencing. Intronic oligonucleotide primers were designed using the PRIMER program (HGMP resource center, MRC Clinical Research Center). An ammonium acetate salting-out procedure was used to isolate genomic DNA from whole blood, as described previously.[4] Both polymerase chain reaction and SSCP analysis were performed using previously described methods.[5] All samples demonstrating an SSCP

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TABLE 1. Clinical and Echocardiographic Features of Patients

	Patients <40 Years (n=74)	Patients ≥40 Years (n=79)	P
Age at diagnosis, y (range)	25.9±9.2 (8–39)	52.9±7.7 (40–71)	
Family history of HCM, n (%)	32 (43)	12 (15)	0.0001
Dyspnea, n (%)			
NYHA 1	55 (74)	52 (66)	0.25
NYHA 2	18 (24)	26 (33)	0.24
NYHA 3	1 (1)	1 (1)	0.96
Chest pain, n (%)			
Exertional	4 (5)	8 (10)	0.28
Atypical	13 (18)	24 (30)	0.064
Both	9 (12)	4 (5)	0.12
Palpitations, n (%)	16 (22)	19 (24)	0.72
Syncope, n (%)	8 (11)	7 (9)	0.69
LVWT, mm	23±7	19±4	0.25
LV end-diastolic diameter, mm	44±9	46±5	0.29
LV end-systolic diameter, mm	25±9	27±5	0.37
Left atrium, mm	43±11	45±6	0.53
Gradient≥30 mm Hg, n (%)	13 (18)	26 (33)	0.03
Pattern of LVH, n (%)			
Asymmetric	50 (68)	45 (57)	0.18
Concentric	8 (11)	20 (25)	0.02
Distal	3 (4)	6 (8)	0.35
Other	13 (18)	8 (10)	0.18
NSVT, n (%)	15 (20)	33 (42)	0.0042

Data shown as mean±SD or number (percent).

NYHA indicates New York Heart Association class; LVWT, maximum left ventricular wall thickness; LV, left ventricular; and NSVT, nonsustained ventricular tachycardia.

variation were directly sequenced using Dynal bead (Dynal) DNA strand separation and the Sequenase II kit (USB).[4]

Statistical Analysis

The χ^2 test was used to compare noncontinuous variables, and the 2-tailed unpaired t test was used to compare continuous variables. Statistical significance was defined as $P<0.05$.

Results

Baseline clinical data are summarized in Table 1. A total of 5 of 79 patients (6.3%) diagnosed at ≥40 years and 1 of 74 patients (1.4%) diagnosed at <40 years had low α-Gal activity (range 0.1 to 0.7 nmol · h^{-1} · mL^{-1}). α-Gal activity in the remaining 147 patients was 7.4±2.7 nmol · h^{-1} · mL^{-1} (range, 2.3 to 25.0 nmol · h^{-1} · mL^{-1}). Plasma α-Gal activity in the 89 controls was 8.4±2.4 nmol · h^{-1} · mL^{-1} (range, 4.8 to 17.6 nmol · h^{-1} · mL^{-1}). All 6 patients with low α-Gal activity had cardiovascular symptoms at presentation. None had a family history of cardiomyopathy or Anderson-Fabry disease. All were normotensive, and 2 had an elevated serum creatinine. Retrospective clinical examination revealed angiokeratoma and acroparaesthesia in 1 patient (patient 3). Five of the 6 patients had undergone coronary angiography; 4 had angiographically normal coronary arteries, and one had a 50% stenosis in the circumflex artery (patient 1).

All 6 patients with low α-Gal activity had an abnormal ECG (Table 2 and Figure 1). One patient (patient 6) had been paced for symptomatic second-degree heart block and was in atrial fibrillation. The ECGs in the remaining 5 patients all met Romhilt-Estes[6] criteria for LVH. Two patients had one or more episodes of nonsustained ventricular tachycardia during Holter monitoring.

The echocardiographic features in the patients with Anderson-Fabry disease are shown in Table 3. Maximum left ventricular wall thickness was 21±4 mm (range, 14–26 mm). Five had concentric hypertrophy (Figure 2), and one had asymmetric septal hypertrophy (patient 6). One patient had systolic anterior motion of the mitral valve and a left ventricular outflow tract gradient of 80 mm Hg (patient 4).

Genetic Analysis

Patients 1, 4, and 5 had the same missense mutation in exon 5 (an adenine to guanine transition at position 644, leading to the substitution of serine for asparagine at residue 215). Patient 2 had a novel thymidine-to-cytosine transition at position 950 in exon 6, resulting in the substitution of threonine for isoleucine at residue 317. Patient 6 had a guanine-to-thymidine transition at nucleotide 937 in exon 6

TABLE 2. Clinical Characteristics and Electrocardiographic Features in Patients With Anderson-Fabry Disease

Patient	Age,* y	α-Gal, nmol · hr^{-1} · mL^{-1}	Chest Pain	NYHA Class	Syncope	Palpitations	PR, ms	QRS, ms	Romhilt-Estes Score	ST-T Changes	NSVT
1	51	0.1	+	2	+	+	152	156	7	+	+
2	34	0.1	−	1	+	+	160	152	13	+	−
3	51	0.3	−	1	−	+	124	104	7	+	−
4	81	0.4	+	2	−	+	144	144	9	+	+
5	42	0.6	+	2	−	−	192	92	11	+	−
6	57	0.7	−	2	−	+	AF	Paced	Paced	Paced	−

*Age at time of study.
AF indicates atrial fibrillation; +, positive; and −, negative. Other abbreviations as in Table 1.

of the coding sequence, which predicted a substitution of tyrosine for aspartic acid at residue 313. Patient 3 had a novel single base pair deletion at position 1223, predicting a frameshift in the reading frame at amino acid 408 and premature termination of translation of the protein product.

Discussion

Clinical features of Anderson-Fabry disease usually appear in childhood and adolescence. As patients age, cardiovascular disease, including conduction abnormalities, cardiomyopathy, and stroke, become a major cause of morbidity.[7] Several reports have suggested that some male hemizygotes remain asymptomatic for most of their adult life. In a study of 1603 men undergoing echocardiography, Nakao and colleagues[2] identified 230 individuals with a left ventricular wall thickness of at least 13 mm, of whom 7 (3%) had α-Gal deficiency. Notably, 6 of the 7 were said to have unexplained hypertrophy. The wider significance of these findings was, however, uncertain because the prevalence of unexplained hypertrophy was unusually high (3% compared with estimates of between 1/500 and 1/1000 in most population studies).[8]

Comparison of Anderson-Fabry Disease and Familial HCM

Most patients with familial HCM have asymmetrical septal hypertrophy (ASH).[3] In contrast, 5 of the 6 patients with low α-Gal activity in this study had concentric hypertrophy. These data are consistent with a recent study of 30 patients with Anderson-Fabry disease; 37% of these patients had concentric LVH, 10% had ASH, and 3% had an eccentric pattern of hypertrophy.[9] In 25% of patients with familial HCM, ASH is associated with dynamic subaortic obstruction.[10] In the present study, one patient with Anderson-Fabry disease had a typical outflow gradient in association with concentric hypertrophy.

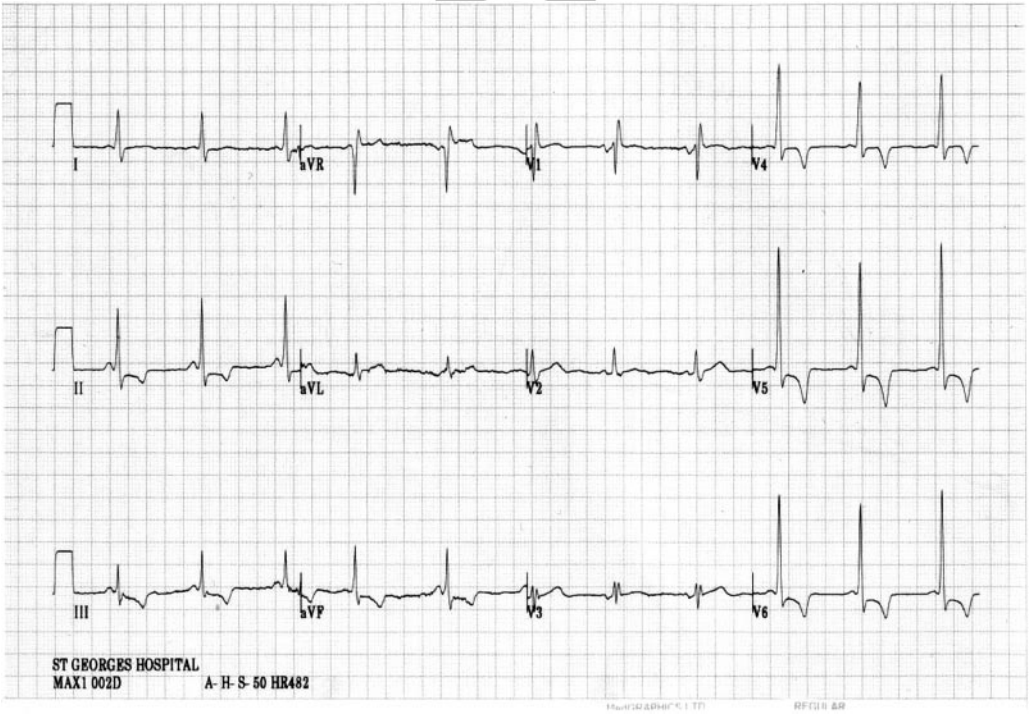

Figure 1. ECG showing LVH and repolarization changes in a patient with Anderson-Fabry disease.

TABLE 3. Echocardiographic Features in Anderson-Fabry Patients

Patient	LVWT, mm	LA, mm	LVED, mm	LVES, mm	Pattern	E Wave, m/s	A Wave, m/s	IVRT, ms	Deceleration Time, ms	Fractional Shortening, %	Valve Abnormalities
1	21	46	50	33	Concentric	0.9	0.7	72	158	34	Normal
2	24	56	52	30	Concentric	0.6	0.5	90	216	42	Normal
3	20	46	53	27	Concentric	0.9	0.5	81	233	49	Mild MR
4	26	44	47	31	Concentric	0.6	1.0	130	147	34	Mild MR, AR
5	14	34	44	26	Concentric	0.7	0.7	88	264	41	Mild MR
6	19	47	40	28	Asymmetric	1.0	Paced/AF	84	193	30	Normal

LVWT indicates maximum left ventricular wall thickness; LA, left atrium; LVED, left ventricular end-diastolic dimension; LVES, left ventricular end-systolic dimension; AF, atrial fibrillation; IVRT, isovolumic relaxation time; MR, mitral regurgitation; and AR, aortic regurgitation.

Many electrocardiographic abnormalities have been described in Anderson-Fabry disease, including short PR intervals and prolonged QRS duration. Both are also described in familial HCM.[11] With regard to arrhythmia, one patient with low α-Gal activity had permanent atrial fibrillation and 2 had nonsustained ventricular tachycardia on Holter monitoring. The prevalence and clinical significance of these arrhythmias in Anderson-Fabry disease cannot, however, be determined from the present study.

Clinical Implications

The present study demonstrates that, as a cause for HCM, Anderson-Fabry disease is at least as common as some sarcomeric protein gene mutations.[1] It should be suspected in male patients with concentric hypertrophy and no family history of HCM or inheritance consistent with X-linked disease. Correct diagnosis is important because recent advances in the treatment of Anderson-Fabry disease may offer stabilization and reversal of some cardiovascular manifestations.[12,13]

Limitations

In view of the X-linked recessive inheritance of Anderson-Fabry disease, we only screened male patients. Although female heterozygotes can also present with cardiac involvement, biochemical diagnosis can be problematic because they often have intermediate levels of enzyme activity overlapping with those seen in normal controls.

The normal controls in this study were Japanese. Although this raises the possibility of ethnic differences, the α-Gal levels used to define Anderson-Fabry disease conform with those used in Western populations.

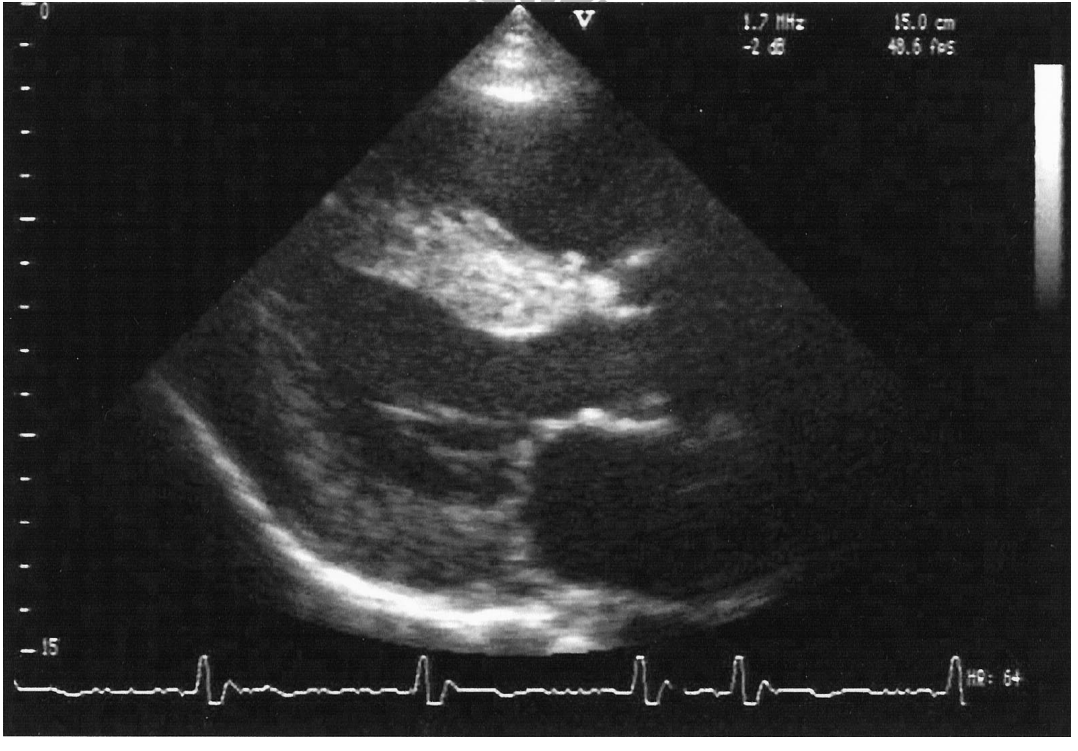

Figure 2. Two-dimensional echocardiograph in the parasternal long-axis view demonstrating concentric LVH in a patient with Anderson-Fabry disease.

References

1. Spirito P, Seidman CE, Mckenna WJ, et al. The management of hypertrophic cardiomyopathy. *N Engl J Med*. 1997;336:775–785.
2. Nakao S, Takenaka T, Maeda M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med*. 1995; 333:288–293.
3. Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide angle two-dimensional echocardiographic study of 125 patients. *Am J Cardiol*. 1981;48:418–428.
4. Davies JP, Winchester BG, Malcolm S. Sequence variations in the first exon of alpha-galactosidase A. *J Med Genet*. 1993;30:658–663.
5. Davies JP, Winchester BG, Malcolm S. Mutational analysis in patients with the typical form of Anderson-Fabry disease. *Hum Mol Genet*. 1993; 2:1051–1053.
6. Romhilt DW, Estes EH Jr. A point-score system for the ECG diagnosis of left ventricular hypertrophy. *Am Heart J*. 1968;75:752–758.
7. Desnick RJ, Ioannou YA, Eng CM. α-Galactosidase, a deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The Metabolic and Molecular Basis of Inherited Disease*. 7th ed. Vol 2. New York: McGraw-Hill; 1995:2741–2784.
8. Maron BJ, Gardin JM, Flack JM, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CARDIA Study. *Circulation*. 1995;92:785–789.
9. Linhart A, Palecek T, Bultas J, et al. New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J*. 2000;139: 1101–1108.
10. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy: the importance of the site and extent of hypertrophy: a review. *Prog Cardiovasc Dis.* 1985;28:1–83.
11. Savage DD, Seides SF, Clark CE, et al. Electrocardiographic findings in patients with obstructive and non-obstructive hypertrophic cardiomyopathy. *Circulation*. 1978;58:402–409.
12. Schiffmann R, Kopp JB, Austin HA 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA*. 2001;285: 2743–2749.
13. Eng CM, Guffon N, Wilcox WR, et al, for the International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med*. 2001;345:9–16.