European Heart Journal (2010) **31**, 1088–1097
doi:10.1093/eurheartj/ehp588

Cardiovascular manifestations of Fabry disease: relationships between left ventricular hypertrophy, disease severity, and α-galactosidase A activity

Justina C. Wu[1]*, Carolyn Y. Ho[1], Hicham Skali[1], Rekha Abichandani[2], William R. Wilcox[3], Maryam Banikazemi[4†], Seymour Packman[5], Katherine Sims[6], and Scott D. Solomon[1]

[1]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA; [2]Genzyme Corporation, Cambridge, MA, USA; [3]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [4]Department of Human Genetics, Mount Sinai School of Medicine, New York, NY, USA; [5]Department of Pediatrics, Division of Medical Genetics, University of California, San Francisco, CA, USA; and [6]Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA

Received 3 November 2008; revised 17 June 2009; accepted 12 October 2009; online publish-ahead-of-print 7 January 2010

Aims Fabry disease is a rare X-linked deficiency of α-galactosidase A (αgal), which causes glycosphingolipid accumulation. This study analysed the cardiovascular manifestations of a cohort of Fabry patients, and sought to define relationships between disease severity, αgal activity, and cardiac abnormalities.

Methods and results We prospectively analysed Fabry patients (139 subjects: 92 males and 47 females) undergoing screening for potential enzyme replacement therapy. Baseline echocardiograms, electrocardiograms, and exams were obtained as part of two multinational clinical trials. Cardiovascular symptoms were present in 60.4%. By echocardiography, the mean left ventricular mass index (LVMI) was increased at 165.5 ± 66.9 g/m^2, and 84.8% of patients displayed concentric left ventricular hypertrophy (LVH). Electrocardiographic LVH was present in >50% of adult subjects. In females, log-corrected plasma αgal activity was inversely associated with LVMI ($r = -0.45$, $P < 0.040$). Males with extremely low αgal activity and renal disease displayed the most LVH and cardiac symptoms, but LVH was prevalent even in females <20 years old.

Conclusion Concentric LVH was the predominant cardiac pathology seen in patients with Fabry disease, and was prevalent in both genders by the third decade of life. Left ventricular mass index was inversely correlated with αgal activity, but was prevalent even in younger females.

Keywords Cardiomyopathy • Echocardiography • Genetics • Hypertrophy • Fabry • α-Galactosidase

Introduction

Fabry disease is a lysosomal storage disorder due to a rare X-linked recessive mutation in the gene encoding the enzyme α-galactosidase A (αgal), although carrier (heterozygous) females may also be affected to varying degrees because of random X-chromosomal inactivation.[1] The progressive deposition of glycosphingolipids can lead to early death due to infiltrative and occlusive disease of the heart, kidney, and brain. Although presenting symptoms may be extracardiac, mortality due to myocardial infarction, arrhythmias, stroke, and renal dysfunction is common.[1–3]

Previous studies addressing the cardiac manifestations of Fabry disease have relied on historical registry data[2–5] or been restricted

† Present address. Department of Neurology, New York University School of Medicine, New York, NY, USA.
* Corresponding author. Tel: +1 617 732 7850, Fax: +1 617 264 5199, Email: jcwu@partners.org

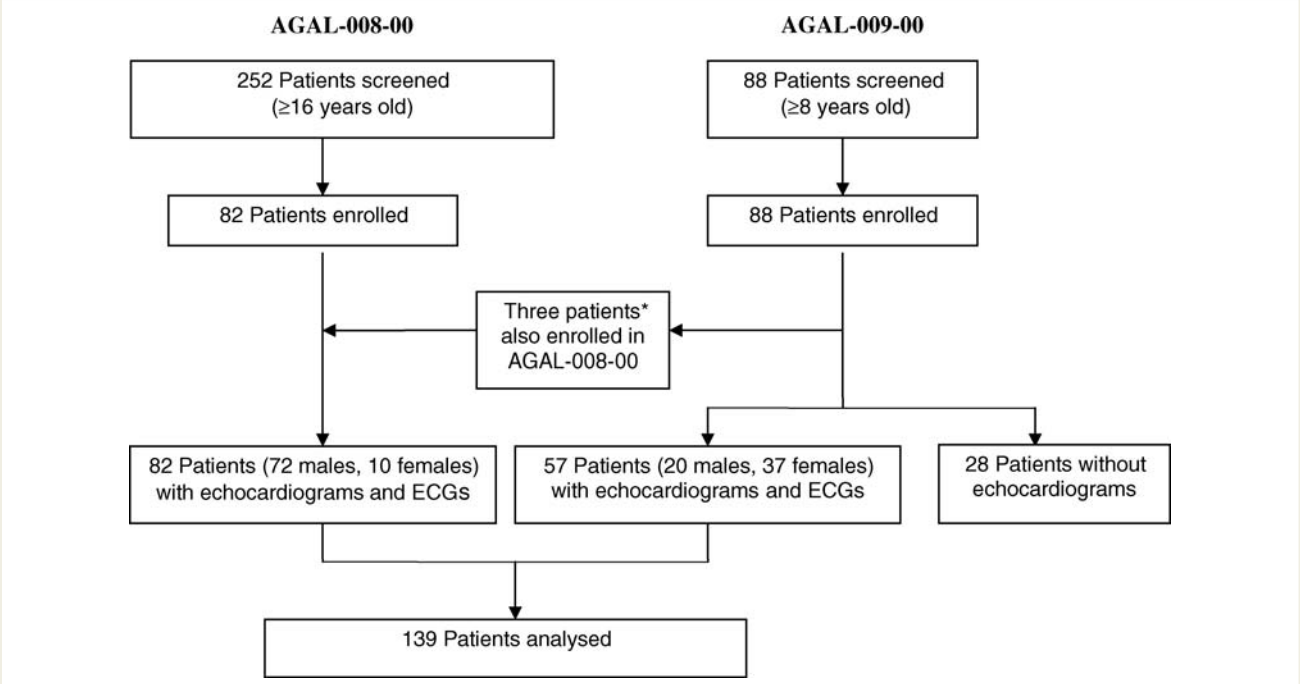


Figure 1 Diagram of Fabry cohorts for cardiovascular analysis. *AGAL-008-00 and AGAL-009-00 studies enrolled concurrently at some centres. Three subjects who were enrolled in both studies were analysed solely as AGAL-008-00 subjects.

to highly selected populations[6–8] and may not accurately represent the entire spectrum or incidence of cardiac disease. Expression of the disease varies: hemizygous males with low residual enzyme activity often display severe manifestations, whereas heterozygous females may range from mild, late-onset to severely affected phenotypes. Systolic and diastolic dysfunction, hypertrophic and restrictive cardiomyopathies, and valvular and conduction system abnormalities have been variably ascribed to Fabry disease.[1–8] We prospectively examined the clinical characteristics with respect to echocardiograms and αgal activity of a large multinational cohort of Fabry disease patients enrolled in either a Phase IV trial designed to evaluate enzyme replacement therapy (ERT) in patients with advanced disease[9] or a screening study designed to identify potential subjects for this trial.

Methods

Study population

Figure 1 is a flowchart of the 139 subjects analysed in the present report, comprising 82 participants from the AGAL-008-00 study and 57 from the AGAL-009-00 study. AGAL-008-00 was a multinational, placebo-controlled Phase IV trial of ERT (Fabrazyme®, agalsidase beta) in Fabry patients with moderately advanced renal disease. AGAL-009-00 was a pre-screening non-interventional study to characterize and identify potential subjects for the Phase IV trial. Between December 2000 and March 2003, physicians experienced in treating Fabry disease screened patients for one or both studies at 38 sites in North America, Europe, Australia, and Israel. All participants provided informed consent in accordance with their institutions' Institutional Review Board or Independent Ethics Committee, and study conduct was in accordance with the Declaration of Helsinki.

For AGAL-008-00, 82 patients (72 males and 10 females) were enrolled. The main inclusion criteria included: (i) ≥16 years old, (ii) a current diagnosis of Fabry disease with no prior treatment with recombinant human αgal, (iii) a clinical presentation consistent with Fabry disease, (iv) documented αgal activity <1.5 nmol/h/mL plasma or <4 nmol/h/mg in leucocytes, and (v) mild-to-moderate renal disease, defined as a serum creatinine (Cr) of 1.2–3.0 mg/dL or an estimated Cr clearance <80 mL/min, if Cr was <1.2 mg/dL. All 82 patients had echocardiograms and electrocardiograms (ECGs) performed as baseline assessment. On the basis of historical values obtained at screening, the mean ± standard deviation (SD) plasma αgal activity was 1.0 ± 0.57 nmol/h/mL for 45 of the patients, and the mean ± SD leucocyte αgal activity was 2.2 ± 1.52 nmol/h/mg for the other 37 patients.

For AGAL-009-00, 88 patients were screened and enrolled. The main inclusion criteria were: (i) ≥8 years old, (ii) a current diagnosis of Fabry disease with no prior treatment with recombinant human αgal, and (iii) a clinical presentation consistent with Fabry disease. Three patients were subsequently enrolled in AGAL-008-00 and are evaluated as part of that study cohort. Of the remaining patients, 57 (20 males and 37 females) had echocardiograms and ECGs performed as part of the screening and were included in this analyses. Thirty-seven patients (65%) were classified as 'confirmed' during the study: 35 patients (all 20 males and 15 females) had a confirmatory genotype and/or enzyme activity criteria (αgal activity level ≤2.4 nmol/h/mL in plasma or <46 nmol/h/mg in leucocytes); two females had a confirmatory genotype with no recorded αgal data; and 20 females had a clinical diagnosis of Fabry disease with plasma αgal levels of 2.5–15.0 nmol/h/mL. Of these 20, at least 18 underwent were subsequently confirmed to have a familial Fabry mutation after study conclusion (W.R.W. *et al.*, personal communication); genotype information on the remaining two

females is unavailable. Thus, for the overall cohort (*Figure 1*), >98% had a genotype and/or αgal activity consistent with Fabry disease.

Echocardiography

Study protocols for both AGAL-008-00 and AGAL-009-00 specified that echocardiograms with standard machines (per individual site preference, settings optimized for endocardial definition) be performed within 28 days of screening. Measurements were made from 2D images by a Level III-certified echocardiologist blinded to all clinical data, using the mean of three cardiac cycles and conventions of the American Society of Echocardiography.[10] Segmental wall thickness was assessed by tracings of the endocardial and epicardial circumferences of basal short-axis images at end-diastole, using the Wyatt convention.[11]

Left ventricular volumes at end-diastole (LVEDV) and end-systole (LVESV) were determined by modified 2D Simpson's formula. Stroke volume (SV) was calculated as [LVEDV − LVESV], and left ventricular ejection fraction (EF) as [SV/LVEDV]. Left ventricular mass was calculated[10] and indexed to body surface area to obtain the left ventricular mass index (LVMI). Relative wall thickness (RWT), or eccentricity, was calculated as [(IVS + PWT)/LVEDD].

Clinical data

At screening, serum Cr was measured and estimated glomerular filtration rate (GFR) was calculated by the Modification of Diet in Renal Disease Study Group equation[12] [186 × (serum Cr in mg/dL)$^{-1.154}$ × (age in year)$^{-0.203}$ × (0.742, for females) × (1.212, if patient ethnicity is African-American). Each patient underwent a review of systems including the presence of symptoms potentially associated with Fabry disease, a cardiovascular assessment, and ECG analysis as listed in *Table 2*.[13]

Statistical analyses

Statistical analyses were performed with STATA 9.1. Data are expressed as mean ± SD. Differences between genders were analysed using the unpaired Student *t*-test with unequal variance (continuous variables with normal distribution), Mann–Whitney *U* test (continuous variables with skewed distribution), and Pearson χ^2 test (dichotomous variables). Least square linear regression analysis was performed to assess bivariate correlations. Multivariate analysis was utilized to correct for all factors identified as significant influences by univariate testing. Differences were considered statistically significant for two-tailed *P*-values <0.05.

Results

Demographics and key clinical characteristics of Fabry cohorts

Table 1 summarizes the demographics of the cohort, stratified by gender. The combined study cohort consisted of 139 unique patients, ranging from 13 to 75 years old (mean age 43.1 years) and approximately two-thirds were male. When compared with the females, the males displayed onset of symptoms at an earlier age, lower αgal levels, and higher serum Cr. And 30% of the total study population was hypertensive at the time of enrollment.

Signs and symptoms associated with Fabry disease and decreased α-galactosidase A activity

As shown in *Table 2*, a majority (60.4%) of the Fabry cohort had a history of abnormal cardiovascular signs and symptoms:

Table 1 Demographics of Fabry cohorts combined from AGAL-009-00 and AGAL-008-00

Parameter	All patients	Male	Female	M vs. F, *P*-value
Number of patients (%)	139 (100%)	92 (66.2%)	47 (33.8%)	
Age (year), mean ± SD (range)	43.1 ± 12.6 (13.1–75.2)	41.9 ± 12.1 (13.1–75.2)	45.4 ± 13.3 (13.4–71.9)	<0.129
Age at onset of Sx[a], mean ± SD	13.8 ± 11.9	12.1 ± 11.6	17.3 ± 12.0	**<0.017**
Age at Dx, mean ± SD	29.8 ± 17.6	30.1 ± 15.9	29.0 ± 20.9	<0.871
Disease duration[b], mean ± SD	28.2 ± 13.7	29.0 ± 12.7	26.5 ± 15.7	<0.387
Ethnicity, *n* (%)				
Caucasian	126 (90.7%)	84 (91.3%)	42 (89.4%)	<0.710
Non-caucasian	13 (9.3%)	8 (8.7%)	5 (10.6%)	
αGal activity[c], mean ± SD (range) *n*				
Plasma (nmol/h/mL)	2.10 ± 2.09 (0–15.0) 97	1.18 ± 0.95 (0–6.7) 54	3.26 ± 2.53 (0.7–15.0) 43	**<0.001**
Leucocyte (nmol/h/mg)	2.18 ± 1.54 (0–4.0) 40	2.10 ± 1.53 (0–4.0) 38	3.70 ± 0.46 (3.6–3.8) 2	**<0.020**
Haemoglobin (g/dL), mean ± SD	1.40 ± 0.89	1.63 ± 0.51	0.92 ± 0.46	**<0.001**
Estimated GFR (mL/min), mean ± SD	71.1 ± 36.5	64.5 ± 37.1	84.4 ± 31.4	0.683
Mean BP (mm Hg), mean ± SD	109 ± 14	109 ± 13	108 ± 15	<0.531
ACE-I or ARB use, *n* (%)	37 (26.6%)	25 (27.2%)	12 (25.5%)	<0.836

[a]Patient age on date of first reported Fabry symptoms listed in *Table 2*.
[b]Time from first onset of symptoms to patient age at screening.
[c]Levels of αgal activity at time of screening are based on historical documentation of either plasma or leucocyte activity; reference ranges for individual historical screening sites may vary.
Bold values indicate $P \leq 0.05$.

Table 2 Clinical signs and symptoms in Fabry cohorts combined from AGAL-009-00 and AGAL-008-00

Clinical signs and symptoms	Number (%) of patients			M vs. F, *P*-value
	All, 139 (100)	Male, 92 (66.2)	Female, 47 (33.8)	
Cardiovascular (any of the following)[a]	84 (60.4%)	61 (66.3%)	23 (48.9%)	**<0.048**
Dyspnoea	23 (16.5%)	15 (16.3%)	8 (17.0%)	<0.914
Angina	15 (10.8%)	8 (8.7%)	1 (2.1%)	<0.137
Chest pain	9 (6.5%)	12 (13.0%)	3 (6.4%)	<0.231
Oedema	39 (28.1%)	35 (38.0%)	4 (8.5%)	**<0.021**
Hypertension	43 (30.9%)	27 (29.3%)	16 (34.0%)	<0.571
Hypotension	4 (2.9%)	3 (3.3%)	1 (2.1%)	<0.071
Murmur	28 (20.1%)	22 (23.9%)	6 (12.8%)	<0.121
ECG abnormalities (any of the following)[a]	88 (63.3%)	72 (78.3%)	16 (34.0%)	**<0.001**
Bradycardia	23 (16.5%)	20 (21.7%)	3 (6.4%)	**<0.021**
Conduction abnormality	26 (18.7%)	21 (22.8%)	5 (10.6%)	**<0.001**
PR < 120 ms	3 (2.1%)	3 (3.3%)	0 (0%)	<0.211
PR > 200 ms	5 (3.6%)	3 (3.3%)	2 (4.3%)	<0.766
RBBB	8 (5.7%)	8 (8.7%)	0 (0%)	**<0.037**
LBBB	1 (0.7%)	1 (1.1%)	0 (0%)	<0.473
Other (IRBB, LAHB)	9 (6.5%)	9 (9.8%)	0 (0%)	**<0.027**
LVH (for ≥35 years old., *n* = 105, 67 M and 38 F)	53 (50.5%)	47 (70.1%)	6 (15.8%)	**<0.001**
RVH	3 (2.2%)	1 (2.1%)	2 (2.2%)	<0.986
Dermatological[b]	116 (83.4%)	83 (90.2%)	33 (70.2%)	**<0.003**
Neural[b]	91 (65.5%)	58 (63.0%)	33 (70.2%)	<0.400
HEENT[b]	87 (62.6%)	57 (62.0%)	30 (63.8%)	<0.829
GI[b]	79 (56.8%)	60 (65.2%)	19 (40.4%)	**<0.005**
Renal[b]	75 (53.9%)	59 (64.1%)	16 (34.0%)	**<0.001**
Musculoskeletal[b]	55 (39.5%)	42 (45.7%)	13 (27.7%)	**<0.040**
Hypercholesterolaemia	25 (18.0%)	17 (18.5%)	8 (17.1%)	<0.832

[a]Hypertension (SBP ≥ 140 or DBP ≥ 90), hypotension (SBP < 90), conduction abnormality (any of the following: short or long PR interval, right bundle branch block, left bundle branch block, other intraventricular conduction delay), left ventricular hypertrophy (LVH), and right ventricular hypertrophy (RVH); LVH criteria (Sokolow–Lyon) were used to examine only subjects ≥35 years old.
[b]Non-cardiovascular review of systems is as follows: Dermatologic (angiokeratomas, hypohydrosis, anhydrosis), HEENT (corneal or lens abnormalities, headache, hypacousia, vertigo), GI (abdominal pain, diarrhoea), Renal (hematuria, proteinuria), Neural (acroparesthesia), Musculoskeletal (arthralgia, myalgia, pain).
Bold values indicate $P \leq 0.05$.

hypertension and oedema were most prevalent, followed by murmur, dyspnoea, and angina. A history of hypotension ($P < 0.04$) or any ECG abnormality ($P < 0.001$) listed in *Table 2* was significantly associated with decreased αgal activity. ECG (Sokolow–Lyon) criteria for left ventricular hypertrophy (LVH) were found in 50.5% of the subjects aged ≥35 years old. Left ventricular hypertrophy by ECG criteria showed a trend ($P < 0.06$) for association with decreased αgal levels after adjustment for mean blood pressure, serum Cr, and estimated GFR.

Table 2 also shows that the most prevalent non-cardiac signs of Fabry disease were dermatological, followed by acroparesthesias, oculosensory dysfunction, gastrointestinal, and renal symptoms. Only two patients had cardiovascular manifestations without any other signs of Fabry disease. The presence of any single dermatological or renal signs in *Table 2* was significantly associated with low αgal levels ($P < 0.01$ for both).

Echocardiographic characteristics and left ventricular geometry of the Fabry cohorts

In the majority of patients, mean LV volumes and diameters, SV, and LV EF were within normal limits compared with reference values from normal standards (*Table 3*).[10] Nine of the 138 (6.5%) subjects had impaired LV systolic function (EF < 55%); all nine were males and most had mild global hypokinesis. Only two patients, one with severe global hypokinesis and one with an apical aneurysm, were noted to have a dilated cardiomyopathy. Approximately one-quarter of the overall population had echocardiographic evidence of right ventricular hypertrophy.

The mean LVMI for the study population is shown in *Table 3*. Increased LV mass (defined as LVMI > 95 g/m^2 for females and >115 g/m^2 for males)[10] was present in the 118 (84.9%) of the subjects. The mean interventricular septum and posterior wall thicknesses were abnormally increased at 1.43 ± 0.39 and 1.40 ±

Table 3 Echocardiographic characteristics of Fabry cohorts (AGAL-009-00 and AGAL-008-00)

	All patients	Male	Female	M vs. F, *P*-value
Number (%) of patients	139[a]	92[a] (66.2%)	47 (33.8%)	
Heat rate (b.p.m.), mean ± SD	66.7 ± 12.9	65.4 ± 12.3	69.5 ± 13.7	<0.132
LVEDV (mL), mean ± SD[a]	96.1 ± 26.19	105.4 ± 25.5	78.5 ± 16.8	**<0.001**
LVESV (mL), mean ± SD[a]	33.7 ± 16.3	38.5 ± 17.2	24.5 ± 8.9	**<0.001**
SV (mL), mean ± SD[a]	66.1 ± 8.19	66.9 ± 14.8	53.9 ± 10.9	**<0.001**
EF (%), mean ± SD[a]	62.4 ± 14.9	64.4 ± 8.4	69.3 ± 6.9	**<0.001**
Pts with EF < 55%[a]	9 (6.7%)	9 (9.8%)	0 (0%)	**<0.027**
LVEDD (cm), mean ± SD	4.39 ± 0.54	4.54 ± 0.524	4.12 ± 0.484	**<0.001**
LVESD (cm), mean ± SD	2.80 ± 0.48	2.89 ± 0.520	2.62 ± 0.344	**<0.001**
IVS (cm)[a], mean ± SD	1.43 ± 0.39	1.49 ± 0.41	1.33 ± 0.34	**<0.024**
PWT (cm)[a], mean ± SD	1.40 ± 0.30	1.42 ± 0.30	1.35 ± 0.30	<0.236
Mean radial WT (cm)[a], mean ± SD	1.45 ± 0.31	1.49 ± 0.31	1.38 ± 0.30	**<0.052**
Relative WT[a] (eccentricity), mean ± SD	0.65 ± 0.18	0.65 ± 0.18	0.67 ± 0.19	<0.642
LV mass (g)[a], mean ± SD	303.4 ± 131.2	332.7 ± 139.1	248.5 ± 94.0	**<0.001**
LVMI (g/m^2)[a], mean ± SD	165.5 ± 66.9	178.7 ± 70.1	140.3 ± 52.5	**<0.001**
RVH, *n* (%)	35 (25.9%)	20 (21.7%)	14 (29.8%)	<0.296
RV hypokinesis, *n* (%)	1 (0.7%)	1 (1.1%)	0 (0%)	ns
LAE (≥mild), *n* (%)	56 (40.3%)	35 (38.0%)	21 (44.7%)	<0.450
RAE (≥mild), *n* (%)	30 (21.6%)	21 (22.8%)	9 (19.1%)	<0.618
Bi-atrial enlargement, *n* (%)	24 (17.3%)	15 (16.3%)	9 (19.1%)	ns
MR (≥moderate), *n* (%)	15 (11.0%)	12 (13.5%)	3 (6.4%)	**<0.024**
AR (>mild), *n* (%)	3 (2.2%)	3 (3.5%)	0 (0%)	ns
Dilated aortic root (>40 mm diameter), *n* (%)	3 (2.1%)	3 (3.3%)	0 (0%)	ns
TR(>mild), *n* (%)	1 (0.7%)	1 (5.3%)	0 (0%)	ns
PASP (mmHg), *n* (%)	31 ± 7.3	31 ± 7.1	31 ± 7.9	ns
n	(*n* = 58, AGAL-009 cohort)	21	37	
Mitral *E* velocity (m/s), *n* (%)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	ns
Mitral *A* velocity (m/s), *n* (%)	0.5 ± 0.2	0.5 ± 0.2	0.6 ± 0.3	
E:*A* ratio, *n* (%)	1.9 ± 0.9	2.2 ± 0.9	1.7 ± 0.8	
TDI *E′* velocity (cm/s), *n* (%)	−11.7 ± 3.6 (*n* = 6)	−14.0 ± 3.6	−9.7 ± 2.3	
E/*E′* ratio, *n* (%)	8.7 ± 2.8	10.3 ± 2.1	7.1 ± 2.5	

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; SV, stroke volume; EF, ejection fraction; IVS, interventricular septal thickness; PWT, posterior wall thickness; WT, wall thickness; RVH, right ventricular hypertrophy; RV, right ventricular; LAE, left atrial enlargement; RAE, right atrial enlargement; MR, mitral regurgitation; AR, aortic regurgitation; TDI, tissue-Doppler imaging (septal); TR, tricuspid regurgitation; PASP, estimated pulmonary artery systolic pressure; ns, non-significant.
[a]The echocardiogram of one male subject was of insufficient quality for accurate 2D measurements.
Bold values indicate $P \leq 0.05$.

0.30 cm, respectively (*Table 3* and *Figure 2*). Of the subjects with increased LVMI, 95.7% had concentric hypertrophy (defined as increased LVMI and RWT > 0.42) and 1.7% had eccentric hypertrophy (i.e. increased LVMI and RWT ≤ 0.42).[12] Three males (2.2%) had an asymmetric hypertrophy with a septal-to-posterior wall thickness ratio of ≥1.5; a significant left ventricular outflow tract gradient and mitral systolic anterior motion was noted in one. Sixteen patients (11.5%) had concentric remodelling (i.e. normal LVMI but RWT > 0.42). Only five patients (3.6%) had normal LV mass and geometry, and these subjects were significantly younger (by 14.5 years, $P < 0.007$) with shorter disease duration (by 12 years, $P < 0.038$) than those with LVH. The overall distribution of LV geometric patterns is shown in *Figure 3*, and illustrates that the vast majority (81.3%) of this Fabry population had concentric LVH.

Notably, over one-third of the patients had left atrial enlargement. Mitral leaflet thickening was seen in 50% of the population and was often associated with moderate or severe mitral regurgitation (*Table 3*). A smaller proportion displayed aortic valve thickening and/or mild aortic insufficiency. There was no clear association of atrial enlargement, valvular abnormalities, or other remaining echocardiographic parameters listed in *Table 3* with αgal activity.

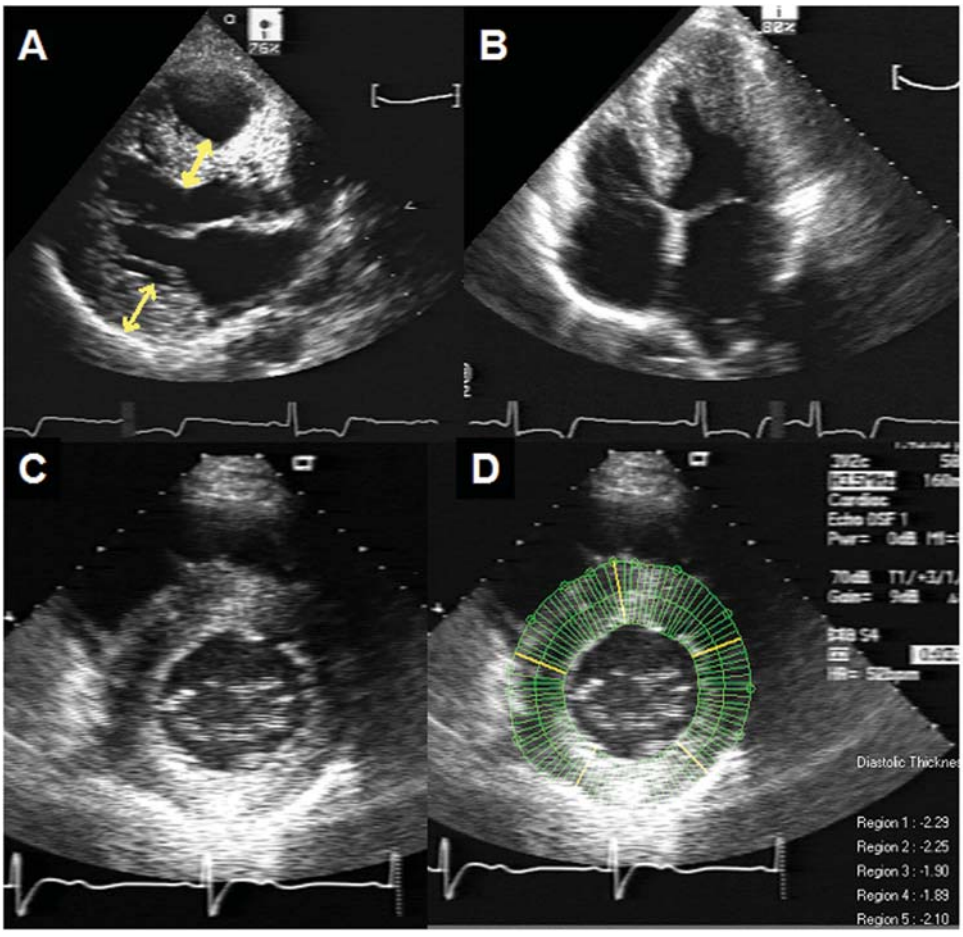


Figure 2 Representative 2D echocardiogram of a 49-year-old male Fabry patient. (*A*) Parasternal long-axis window at end-diastole. Yellow arrows indicate standard ASE measurements of the interventricular septum and posterior wall at the base. (*B*) Apical four-chamber window at end-systole. Severe concentric left ventricular hypertrophy (LVH) and preserved ejection fraction is shown. (*C*) Parasternal short-axis window at end-diastole. (*D*) Radial chord method utilized to measure regional left ventricular wall thickness.

Diastolic function was assessed by mitral inflow Doppler in only the AGAL-009 cohort, with tissue-Doppler data limited to an even smaller subset (*Table 3*). Forty-eight per cent of subjects examined displayed a mitral Doppler pattern suggestive of restrictive disease, with *E:A* ratios of $\geq$2.0. Tissue Doppler data were limited to only a small sample of the AGAL-009 patients, with a mean septal *E′* velocity of -11.8 ± 3.6 cm/s (normal reference value -13 cm/s for mean age of 43 years old),[14] and mean *E/E′* ratio of 8.7 ± 2.8. There was a correlation noted between *E′* velocity and LVMI ($r = -0.91$, $P < 0.013$) in this group, of whom two-third had concentric LVH.

Analysis of the relationship between left ventricular mass index and clinical variables

As increased LV mass was present in almost 85% of the cohort by echocardiography, we investigated the relationships between LVMI, other clinical variables, and plasma αgal activity. In univariate analysis, age, serum Cr, and haemoglobin were directly related to mean wall thickness and LVMI; estimated GFR was inversely correlated with LVMI. Past or present hypertension alone was insufficient to account for differences in LVMI. Only a trend for the use of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) ($P < 0.10$) was noted for association with LVMI. The presence of LVH by both ECG and transthoracic echocardiogram criteria was associated with lower αgal levels ($P < 0.0001$) and a positive history of cardiovascular symptoms ($P < 0.002$).

Most patients had αgal activity measured in plasma than in leucocytes (*Table 1*), so further analyses were conducted for patients with plasma αgal activity. *Figure 4A* shows that in univariate analysis of these 50 patients (19 males and 31 females), enzyme activity was significantly inversely correlated with LVMI ($r = -0.32$, $P < 0.018$). This relationship remained highly significant ($P < 0.001$) after correction for age, estimated GFR, and anaemia. An even stronger relationship between the logarithm of plasma αgal activity and LVMI in the total population ($r = -0.38$ and $P < 0.006$) was observed. However, since all males except one genotypically confirmed subject had plasma

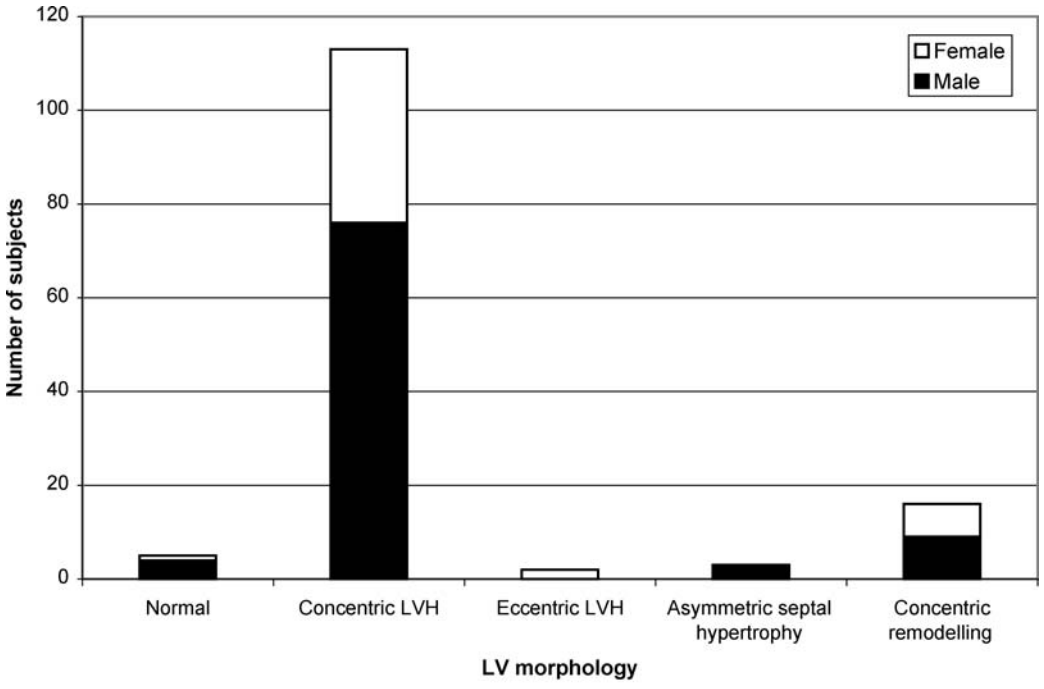


Figure 3 Distribution of left ventricular morphological patterns in Fabry cohorts. P = non-significant for males vs. females of each group.

αgal activity ≤1.5 nmol/h/mL, the correlation was largely observed in females.

A separate analysis of all females with plasma αgal data, shown in *Figure 4B*, revealed a significant inverse correlation of LVMI with log-corrected αgal activity ($r = -0.45$, $P < 0.040$), after correction for age, estimated GFR, and haemoglobin. In this group, taking into account all significant confounders found by univariate analysis, decreased residual αgal activity was independently associated with increased LVMI.

Figure 4C details the age distribution of male and female Fabry subjects with αgal measured by plasma method. Increased LVMI was noted to be present in two of the four females <30 years old, neither of whom had a history of hypertension or anaemia.

Cardiovascular manifestations of Fabry stratified by gender and α-galactosidase A activity

Fabry-associated characteristics were compared in hemizygous males and heterozygous females as shown in *Tables 1–3*. Males had lower αgal activity and manifested symptoms at an earlier age. The incidence and extent of disease, as reflected by renal dysfunction, ECG abnormalities (namely intraventricular conduction abnormalities and LVH), and cardiovascular symptoms, was higher in males. Although the prevalence of LVH by echocardiography was similar between genders, the extent of increase in LVMI was significantly higher in males, and only men exhibited left ventricular systolic dysfunction.

Discussion

Although identified a century ago, Fabry disease remains a challenge to diagnose and treat. Registry data suggest that at least 10% of patients may first present with a cardiac event (www.fabryregistry.com),[5] and that cardiac disease is a leading cause of mortality in affected females.[4,15] Traditional palliative treatments consist of restricted diets and haemodialysis, but ERT is now emerging as potentially effective therapy.[16–18]

In the present cohort of 139 Fabry patients (representing over 21 different mutations), a high prevalence of cardiovascular manifestations was found. Left ventricular hypertrophy was present in up to 41% by ECG and >84% by echocardiography. The presence of LVH in both studies was associated with higher prevalence of cardiovascular symptoms and lower αgal activity. Although males in the cohort had almost uniformly negligible αgal activity and a higher degree of LVH than females, even females <30 years old were detected to have increased LVMI. A small proportion (6.5%) of males had decreased LV systolic function, and of these an even smaller fraction—both AGAL-008-00 males with paced rhythm and no history of angina—had LV dilatation. One of these males, with a 46-year history of symptoms and moderate renal disease, had an LV aneurysm suggestive of more advanced disease and/or fibrosis. In females, a broader range of residual αgal activity was present, and the severity of cardiac hypertrophy was inversely associated with log-corrected αgal activity. These findings suggest that increased LV mass is not merely a secondary response to age, renal failure, or pressure-overload. Accumulation of

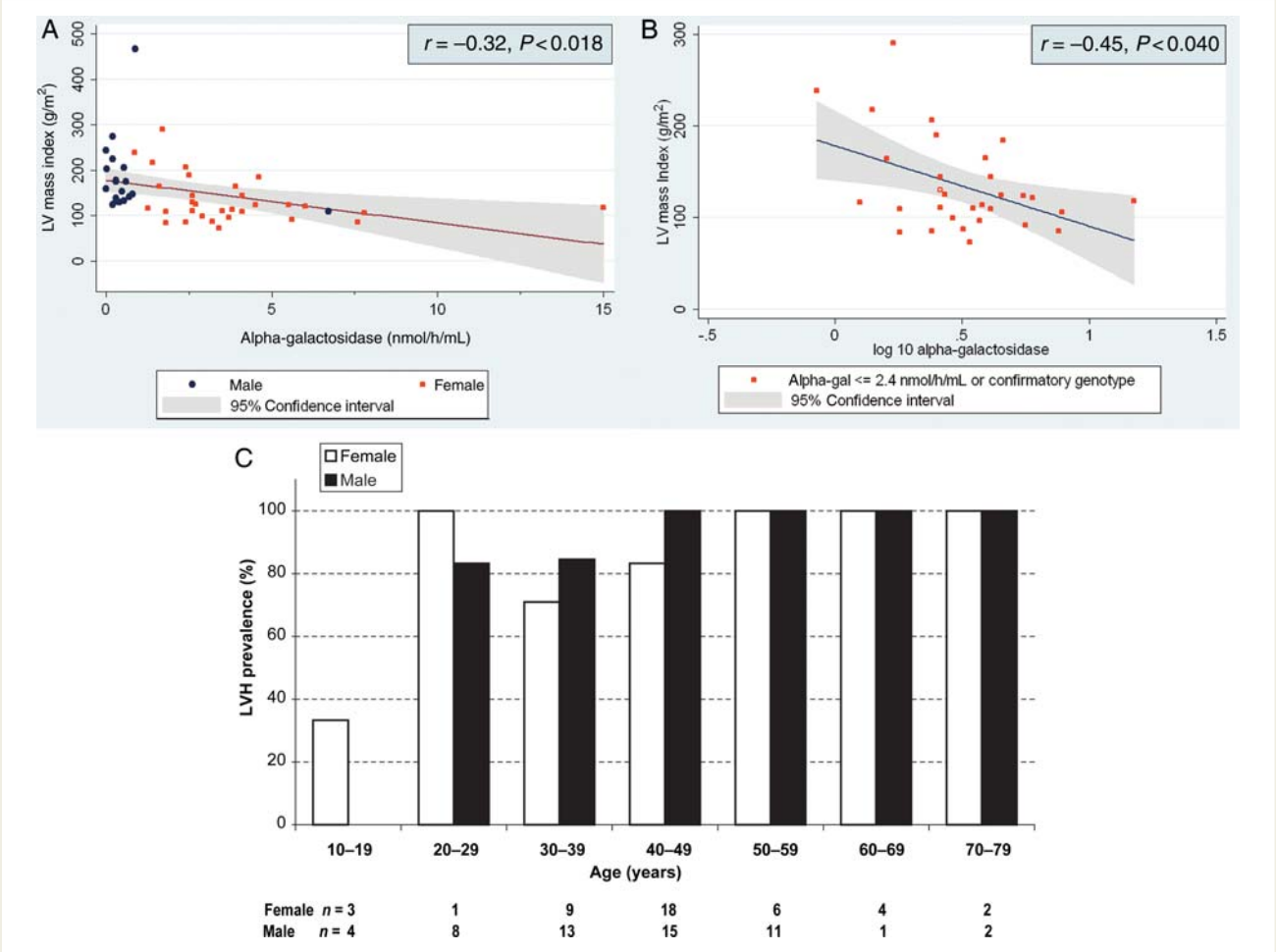


Figure 4 Plasma α-galactosidase activity vs. left ventricular mass index (LVMI) in (*A*) males (n=19) and females (n = 31), and (*B*) females only. Data are shown only for those subjects with αgal activity reported for plasma and measurable LVMI. Subjects with αgal data derived from leucocytes or with activity expressed ambiguously (e.g. ≤1.5 nmol/h/mL) were not included here. Reference ranges for individual historical screening sites may vary. Genotyping information is not currently available for the subject represented by the open square in (B). (*C*) Age distribution of all subjects with increased LVMI and αgal activity assayed in plasma.

glycosphingolipid has been observed microscopically within cardiomyocytes, the microvasculature, and conduction system,[6] and may contribute directly to hypertrophy as well as to valve leaflet thickening. However, the glycosphingolipids have been estimated to constitute <1% of cardiac mass;[19] hence other mechanisms, speculatively neurohormonal, inflammatory, or vasoreactive in nature, must additionally drive organomegaly. No significant correlation of any diastolic parameters (mitral inflow or tissue-Doppler imaging) with αgal activity was found, although septal *E′* velocities were negatively and significantly correlated with LVMI in this small subgroup.

These data provide a large prospective in-depth echocardiographic analysis of a Fabry disease cohort. The study cohort included mostly middle-aged patients with at least mild disease, in which over 60% had cardiovascular manifestations. A high proportion of females with cardiovascular and echocardiographic abnormalities was observed, corroborating registry data.[4,5,15,20] Linhart *et al.*[4] retrospectively surveyed a larger cohort of untreated and ERT-treated Fabry patients and found a similar prevalence of cardiac signs and symptoms but a slightly lower overall frequency of echocardiographic LVH in untreated patients. In the recent largest study of Fabry cardiomyopathy to date, Kampmann *et al.*[21] performed a cross-sectional echocardiographic study of 177 males and females Fabry patients and also found a lower baseline prevalence (48.6% of males and 36.4% of females) of echocardiographic LVH, which may be due to the exclusion of hypertensive or ACE-I/ARB-treated subjects. Their study also found that concentric hypertrophy was the most prevalent cardiomyopathy. In the subset of subjects followed longitudinally, age of onset and progressive LVMI increase appeared slower in females. Our current report extends current registry knowledge, by systematically examining detailed echocardiographic characteristics for association with the αgal activity levels and clinical status. Our results suggest that reduced αgal activity contributes to increased LVMI, ECG abnormalities, and clinical symptoms via mechanisms independent of age, hypertension, ACE-I, and ARB use, renal dysfunction, and anaemia.

Study limitations

A limitation of this study is the lack of a control group consisting of individuals without Fabry disease. Additionally, a majority of patients had moderate renal dysfunction in order to be included in AGAL-008-00; consequently, patients with early disease may be under-represented. The identification of Fabry disease can be problematic and may introduce ascertainment bias, particularly in females who are often initially identified by family history.[4] Although atypical variants with only cardiac manifestations have been reported,[7] only two such subjects were identified here. Because αgal activities for participants in the AGAL studies were based on historical screening data, values could not be normalized to a single reference range. Of note, only two females and less than half of the males had αgal activity measured in leucocytes (which may be more reliable), hence sample size was too small for significant analysis. Finally, tissue-Doppler analysis, which may provide additional information on the diastolic function of Fabry cardiomyopathy,[22] was performed only in a limited number of subjects, since many were screened prior to the widespread use of this technique.

Clinical implications

In summary, the prevalence of cardiovascular signs and symptoms, particularly concentric LVH, is high in this cohort of patients with Fabry disease. Left ventricular hypertrophy was already prevalent in subjects of both genders by the second decade of life. Low αgal activity in Fabry patients appears to be independently associated with the development of cardiac hypertrophy. None of these subjects received ERT, which has now been demonstrated to slow progression of a composite endpoint of renal, cardiac, and central nervous system events in the AGAL-008-00 trial,[9] and in some cases appears to limit the increase in LV mass and wall thickness.[18] Our results confirm and extend findings from recent registry data regarding the high prevalence of cardiac hypertrophy in both Fabry males and females, which increases with age, disease severity, and αgal deficiency and raise the possibility that ERT may need to be instituted early, particularly in females with low αgal activity, in order to significantly alter the course of Fabry cardiomyopathy.

Funding

This work was supported by a research grant from Genzyme Corporation to J.C.W., C.Y.H., H.S., M.B., K.S., S.D.S.; and a GCRC Grant M01-RR00425 to W.R.W.

Conflict of interest: W.R.W. is a consultant to Genzyme, Shire, and Amicus Corporations. S.P. is a consultant to Genzyme, Actelion, and Amicus Corporations. R.A. is an employee of Genzyme Corporation.

The study investigators for AGAL-009-00 were: Gideon Bach, MD, Jerusalem, Israel; David Bodensteiner, MD, Kansas City, KS; Louis Caplan, MD, Boston, MA; Louis Elsas, MD, Miami, FL; Paul Fernhoff, MD, Atlanta, GA; Richard Finkel, MD, Philadelphia, PA; Brian Hutchison, MD, Nedland, Australia; Edwin Kolodny, MD, New York, NY; S.P., MD, San Francisco, CA; David Saltissi, MD, Brisbane, Australia; Prof. David Sillence, Westmead, Australia; K.S., MD, Boston, MA; W.R.W., MD, PhD, Los Angeles, CA.

The study investigators for AGAL-008-00 were: M.B., MD, New York, NY; John A. Barranger, MD, PhD, Pittsburgh, PA; Daniel Bichet, MD, Québec, Canada.; David Bodensteiner, MD, Kansas City, KS; Jan Bultas, MD, Prague, Czech Republic; David Bushinsky, MD, Rochester, NY; Joel Charrow, MD, Chicago, IL; Christine M. Eng, MD, Houston, TX; Richard W. Erbe, MD, Buffalo, NY; Paul Fernhoff, MD, Atlanta, GA; Richard Finkel, MD, Philadelphia, PA; Robert M. Greenstein, MD, Farmington, CT; János Grubits, MD, Sopron, Hungary; Robert J. Hopkin, MD, Cincinnati, OH; Marie McDonald, MD, Durham, NC; S.P., MD, San Francisco, CA; C. Ronald Scott, MD, Seattle, WA; K.S., MD, Boston, MA; Anna Tylki-Szymanska, MD, Warsaw, Poland; Stephen Waldek, MB, BCh, Manchester, UK; David Warnock, MD, Birmingham, AL; Neal Weinreb, MD, Coral Springs, FL; Chester Whitley, PhD, MD, Minneapolis, MN; W.R.W., MD, PhD, Los Angeles, CA; Michael L. West, MD, Halifax, Canada; Philip Wyatt, MD, Toronto, Canada.

References

1. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, Grabowski G, Packman S, Wilcox WR. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann Intern Med* 2003;**138**:338–346.
2. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J Med Genet* 2001;**38**:750–760.
3. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet* 2001;**38**:769–775.
4. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, Elliott PM. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. *Eur Heart J* 2007;**28**:1228–1235.
5. Eng CM, Fletcher J, Wilcox WR, Waldek S, Scott CR, Sillence DO, Breunig F, Germain DP, Nicholls K, Banikazemi M. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *J Inherit Metab Dis* 2007;**30**:184–192.
6. Linhart A, Palecek T, Bultas J, Ferguson JJ, Hrudova J, Karetová D, Zeman J, Ledvinová J, Poupetova H, Elleder M, Aschermann M. New insights in cardiac structural changes in patients with Fabry's disease. *Am Heart J* 2000;**139**:1101–1108.
7. von Scheidt W, Eng CM, Fitzmaurice TF, Erdmann E, Hubner G, Olsen EG, Christomanou H, Kandolf R, Bishop DF, Desnick RJ. An atypical variant of Fabry's disease with manifestations confined to the myocardium. *N Engl J Med* 1991;**324**:395–399.
8. Kampmann C, Baehner F, Whybra C, Martin C, Wiethoff CM, Ries M, Gal A, Beck M. Cardiac manifestations of Anderson-Fabry disease in heterozygous females. *J Am Coll Cardiol* 2002;**40**:1668–1674.
9. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, Finkel R, Packman S, Bichet DG, Warnock DG, Desnick RJ, for the Fabry Disease Clinical Trial study Group. Agalsidase-beta therapy for advanced Fabry disease. *Ann Intern Med* 2007;**146**:77–86.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. *J Am Soc Echocardiogr* 2005;**18**:1440–1463.
111. Wyatt HL, Haendchen RV, Meerbaum S, Corday E. Assessment of quantitative methods for 2-dimensional echocardiography. *Am J Cardiol* 1983;**52**:396–401.
122. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–470.
13. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* 1949;**37**:161–186.
14. Henein M, Lindqvist P, Francis D, Mörner S, Waldenström A, Kazzam E. Tissue Doppler analysis of age-dependency in diastolic ventricular behaviour and filling. *Eur Heart J* 2002;**23**:162–171.
15. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest* 2004;**34**:236–242.
16. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linthorst GE, Desnick RJ, 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.
17. Weidemann F, Breunig F, Beer M, Sandstede J, Turschner O, Voelker W, Ertl G, Knoll A, Wanner C, Strotmann JM. Improvement in cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. *Circulation* 2003;**108**:1299–1301.
18. Hughes DA, Eliott PM, Shah J, Zuckerman J, Coghlan G, Brookes J, Mehta AB. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. *Heart* 2008;**94**:153–158.
19. Elleder M, Bradova V, Smid F, Budesínský M, Harzer K, Kustermann-Kuhn B, Ledvinová J, Bělohlávek, Král V, Dorazilová V. Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease. Report on a case simulating hypertrophic non-obstructive cardiomyopathy. *Virchows Arch A Pathol Anat Histopathol* 1990;**417**:449–455.
20. Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, Sims K, Waldek S, Pastores GM, Lee P, Eng CM, Marodi L, Stanford KE, Breunic F, Wanner C, Warnock DG, Lemay RM, Germain DP. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry. *Mol Gen Met* 2008;**93**:112–129.
21. Kampmann C, Linhart A, Baehner F, Palecek T, Wiethoff CM, Miebach E, Whybra C, Gal A, Bultas J, Beck M. Onset and progression of Anderson-Fabry disease related cardiomyopathy. *Int J Cardiol* 2008;**130**:367–373.
22. Pieroni M, Chimenti C, Ricci R, Sale P, Russo MA, Frustaci A. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. *Circulation* 2003;**107**:1978–1984.

CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehp581
Online publish-ahead-of-print 27 December 2009

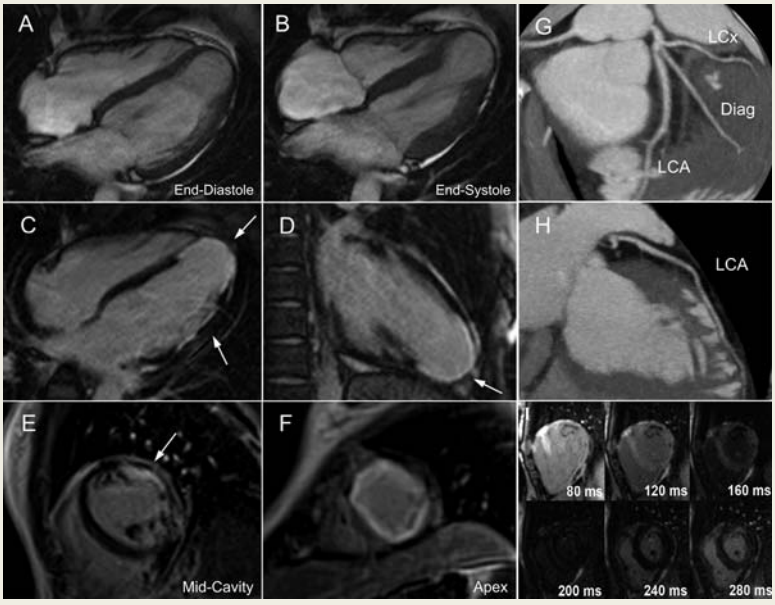
Multiple myocardial infarctions in a 35 year-old woman with POEMS syndrome

Camille Soullier*, Jaime Micolich, and Pierre Croisille

Department of Radiology, Hôpital Louis Pradel, Hospices Civils de Lyon, Lyon, France

* Corresponding author. Tel: +33 683072733, Fax: +33 46722879, Email: camille_soullier@hotmail.com

We report the case of a 35-year-old woman with a POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes). A transthoracic echocardiography was performed to investigate her monoclonal gammopathy, revealing an apical dyskinesia, and diastolic dysfunction. She had no cardiovascular risk factor except a light smoking of 3 pack years; a 12-lead electrocardiogram showed no sign of prior myocardial infarction.



A cardiac magnetic resonance imaging study soon confirmed echocardiography findings: cine sequences demonstrated a significant wall thinning and dyskinesia of all apical segments of the left ventricle (*Panels A* and *B*). Delayed enhancement sequences showed a transmural hyperenhancement in the same apical segments, and a subendocardial hyperenhancement in the lateral wall, of 50% transmural extension, matching the presence of myocardial infarction scars (*Panels C–F*). Ti-Scout sequence showed no blood-pool and myocardial tissue kinetics that could have suggested a co-existing amyloid disease (*Panel I*). Furthermore, a liver biopsy performed because of an elevation of γ-glutamyltransferase showed no evidence of amyloid deposition.

We described with this patient a case of asymptomatic myocardial infarctions in a young woman without relevant risk factors (3 pack years of smoking), and in whom a 64-slice multidetector computed tomography angiography showed no evidence of coronary artery disease (*Panels G* and *H*). In this context, we might relate this thrombotic event to the pro-thrombotic state already described in POEMS syndrome, caused by the elevation of pro-inflammatory cytokines levels such as vascular endothelial growth factor, that was significantly increased in our patient. This pathology is also known to be associated with elevation of circulating matrix metalloproteinase levels, which is implicated in adverse post-infarction remodelling.