Ventricular Septal Myectomy for the Treatment of Left Ventricular Outflow Tract Obstruction Due to Fabry Disease

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Fabry cardiomyopathy can cause symptomatic left ventricular outflow tract obstruction. We review a case of Fabry cardiomyopathy mimicking hypertrophic cardiomyopathy on echocardiography with severe left ventricular outflow tract obstruction treated with ventricular septal myectomy. **(Am J Cardiol 2020;132:160−164)**

Fabry disease (FD) is a lysosomal storage disorder that frequently causes cardiovascular disease in early adulthood and middle age.[1] Dysfunction results from accumulation of glycosphingolipids in the myocardium. Progressive accumulation leads to the development of left ventricular (LV) hypertrophy and in rare circumstances LV outflow tract obstruction. The optimal management of LV outflow tract obstruction in patients with FD cardiomyopathy is unknown. Medical management is usually sufficient, but some patients with FD and LV outflow tract obstruction may require septal reduction therapy. The epidemiology and outcomes of FD patients undergoing septal reduction therapy is not known. This report was prompted by a patient with FD cardiomyopathy mimicking hypertrophic cardiomyopathy (HC) with LV outflow tract obstruction requiring surgical myectomy for symptom management.

Case description

A 38-year-old man presented to our cardiology clinic for cardiovascular evaluation. He initially developed symptoms of peripheral neuropathy and anhydrosis as a child. As an adult, he started developing progressive chronic kidney disease and was eventually diagnosed with FD on kidney biopsy. Over the past 2 years, he had developed progressive dyspnea on exertion and associated chest pressure with exertion.

Genetic testing revealed a missense of the GLA gene, alpha-galactosidase activity level was 0.9 nmol/hr/mg (normal range 12.8 to 74.1 nmol/hr/mg). The serum creatinine was 3.5 mg/dl. Electrocardiogram showed LV hypertrophy, total 12-lead QRS voltage of 213 mm, t-wave inversions, and a short PR interval (Figure 1). Transthoracic echocardiography showed hyperdynamic LV function, severe concentric LV hypertrophy, and a depressed LV global longitudinal strain of −13% (Figure 2). The coronary arteries were angiographically normal. Serial echocardiograms over a 5-year period revealed progressive development of systolic anterior motion of the mitral valve and a worsening LV outflow tract gradient of 64 mm Hg (Figure 3). On a stress echocardiogram LV outflow tract gradient increased from 64 mm Hg at rest to 190 mm Hg at peak exercise. Cardiac magnetic resonance imaging (CMR) showed LV hypertrophy with ventricular septal diameter of 2.4 cm and LV posterior wall thickness of 1.8 cm. Native myocardial T1 values were 875 ms consistent with a cardiac variant of FD (Figure 4).[2]

Due to his history of progressive renal dysfunction over the past 5 years he had been treated with enzyme replacement therapy (ERT). ERT was continued throughout his treatment course.

Despite appropriate medical treatment, the patient continued to have progressive dyspnea on exertion and presyncope. He was considered for kidney transplant due to progressive renal disease but his severe LV outflow tract obstruction made surgery high risk. The decision was made to perform ventricular septal myectomy to help relive his symptoms and allow for future kidney transplantation. During surgery, 4.8 grams of myocardium was removed. He had no significant complications and was discharged home 4 days after the operation. At follow up 3 months later resting gradient on transthoracic echocardiogram was 10 mm Hg, his symptoms had completely resolved, and he was listed for kidney transplantation.

Discussion

FD is a systemic lysosomal storage disorder that occurs due to mutations in the X-linked GLA gene leading to deficiencies in the enzyme alpha-galactosidase and subsequent accumulation of globotriaocylceramide in lysosomes. The clinical presentation of FD can vary greatly between individuals and is related to the levels of residual alpha-galactosidse activity. In males with severe deficiency, patients will classically present in childhood with peripheral neuropathy, angiokeratomas, and renal dysfunction. Almost all patients with classic presentations of FD will go on to develop

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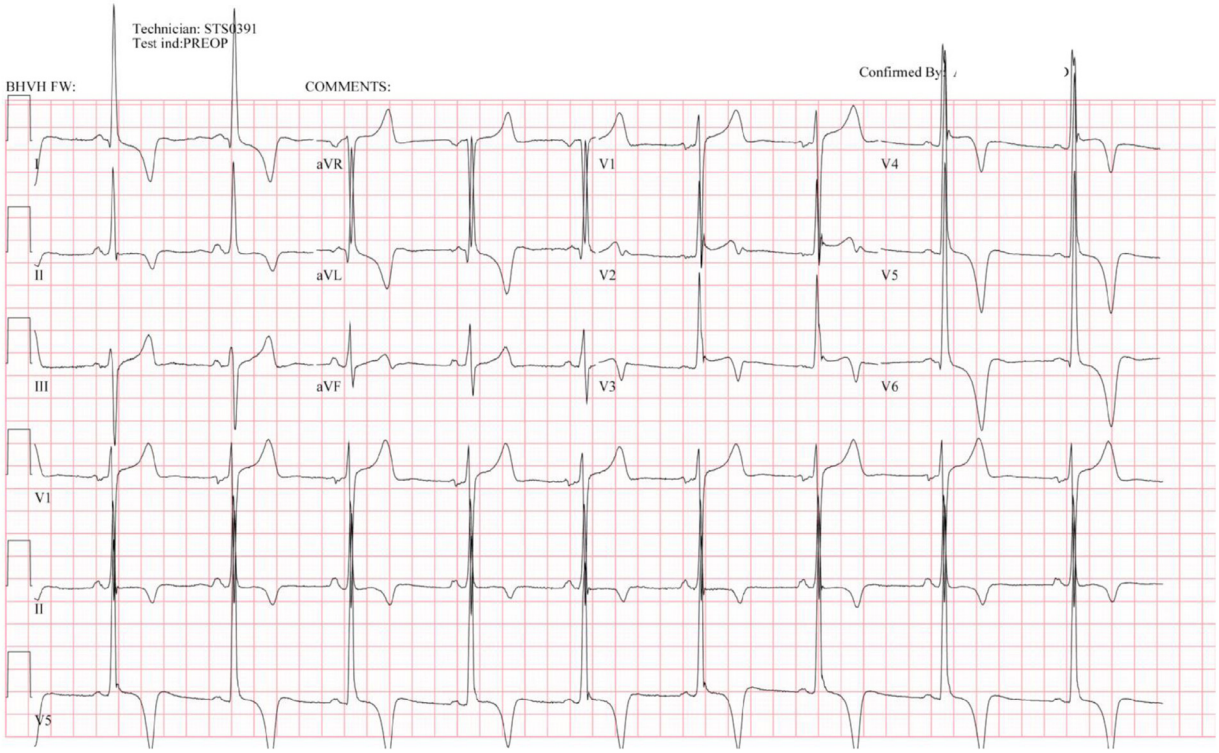

Figure 1. ECG with evidence of LV hypertrophy. Total 12 lead QRS voltage 213 mm. ECG findings in FD can often mimic patients with HC. A short PR interval (136 ms) is often found in patients with FD.[1] FD = Fabry disease; HC = hypertrophic cardiomyopathy; LV = left ventricular.

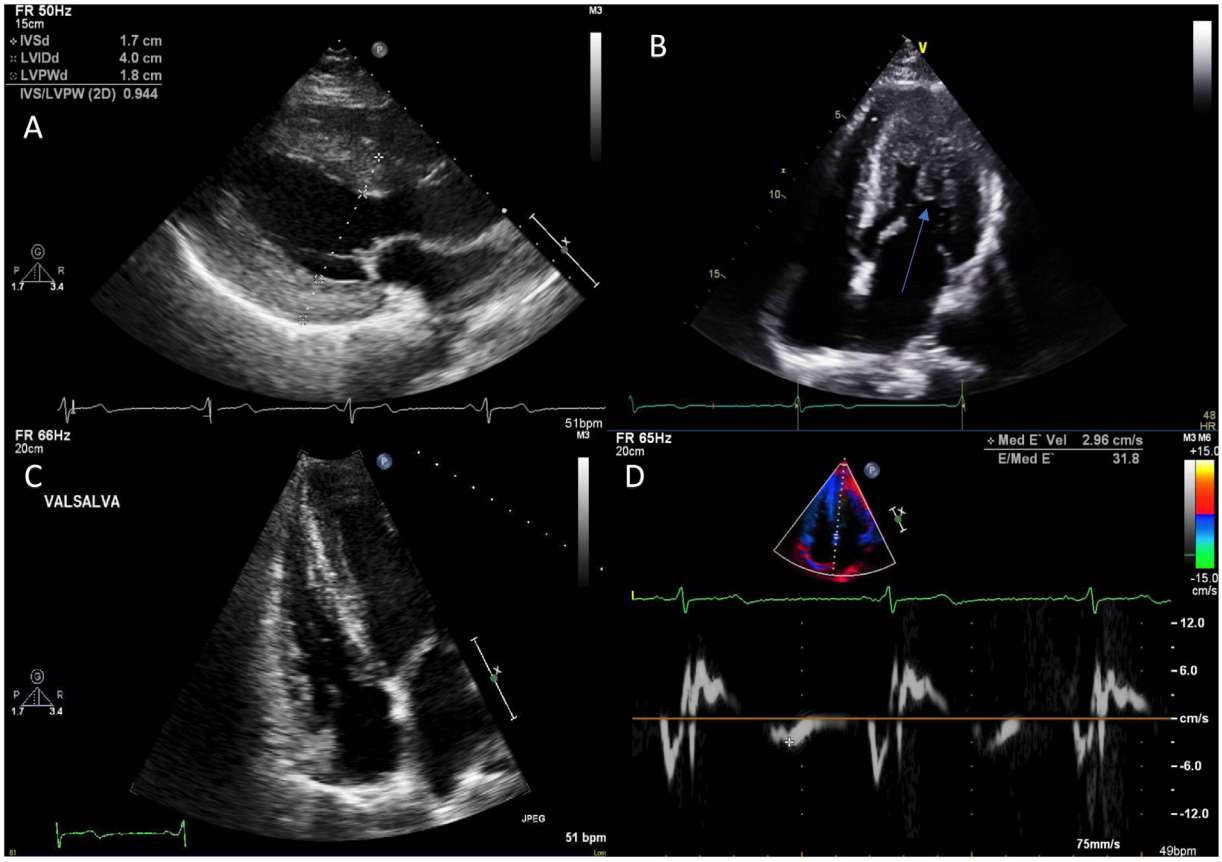

Figure 2. *(A)* Parasternal long axis at end diastole. Interventricular septal diameter 1.7 cm, Left ventricular posterior wall diameter 1.8 cm. *(B)* Note hypertrophic papillary muscle *(blue arrow). (C)* Right ventricular hypertrophy is also present. Biventricular hypertrophy and papillary muscle hypertrophy are both common findings in patients with FD.[13] *(D)* Diastolic dysfunction is common.[13] Medial E' velocity on tissue Doppler is severely reduced to 2.65 cm/s.

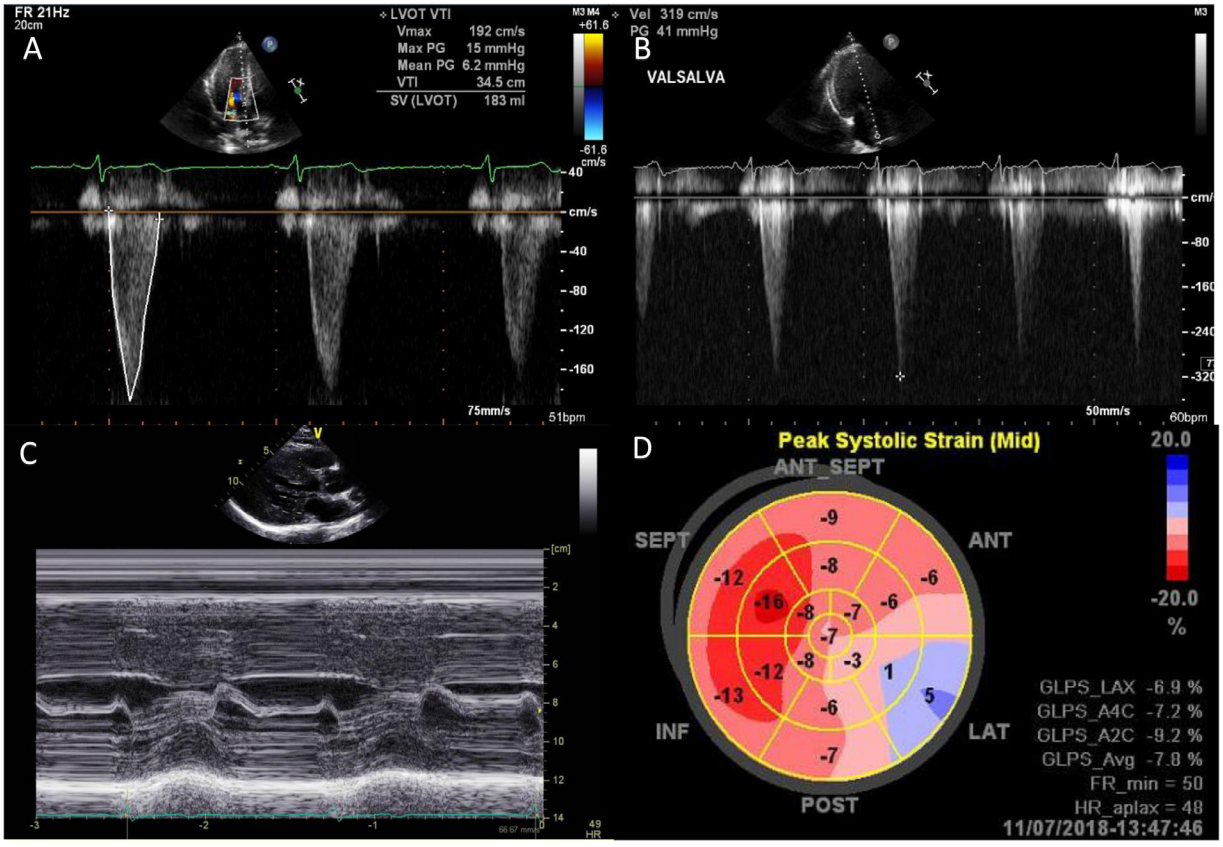

Figure 3. *(A)* Peak resting LV outflow tract gradient 15 mm HG. *(B)* Peak LV outflow tract gradient increased to 41 mm Hg with Valsalva. *(C)* M-mode through the mitral valve shows systolic anterior motion of the mitral valve. *(D)* Abnormal global longitudinal strain is a common feature in FD, even in patients with preserved LV ejection fraction.[4] More positive values indicate areas of decreased longitudinal strain. Fibrosis of the myocardium in FD is commonly found in the basal posterior-lateral wall, reflected here by the markedly abnormal longitudinal strain in this territory. Abnormal longitudinal strain in this territory should always raise suspicion for FD in patients with undifferentiated LV hypertrophy.[4] FD = Fabry disease; LV = left ventricular.

cardiovascular disease presenting as LV hypertrophy in the third and fourth decades of life.[3] Patients with milder enzyme deficiencies and heterozygous females tend to present with isolated cardiac or renal manifestations in the third and fourth decades of life. Patients who develop FD cardiomyopathy are at risk of heart failure, sudden cardiac death, and in rare cases severe LV outflow tract obstruction.

Because of the varied clinical presentation, FD can be challenging to diagnose. Misdiagnosis is especially common with FD cardiomyopathy because on echocardiogram the LV hypertrophy and LV outflow tract obstruction visually resemble HC. Advanced cardiac imaging is required to distinguish HC from FD cardiomyopathy. On echocardiogram, the only characteristic finding for FD is global

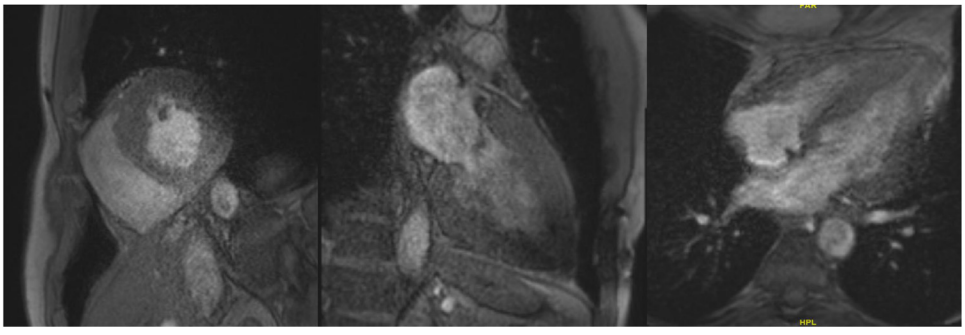

Figure 4. CMR shows severely increased LV wall thickness. Maximal thickness at mid anteroseptum is 2.4 cm, posterior wall thickness is 1.8 cm. Native myocardial T1 Value is reduced at 875 ms. Reduced noncontrast myocardial T1 values are highly sensitive and specific for FD in patients with undifferentiated LV hypertrophy.[2] Gadolinium was not used in this patient due to chronic kidney disease. Patients with FD can have pathologic late gadolinium enhancement. Late gadolinium enhancement is often present in the inferolateral LV wall but atypical patterns can also exist.[4] Biventricular hypertrophy is also noted on CMR. Artifact in lateral wall of the LV. CMR = Cardiac magnetic resonance imaging; FD = Fabry disease; LV = left ventricular.

Table 1.
Previously reported cases of ventricular septal reduction therapy in patients with FD and LV outflow tract obstruction

Patient (Reference)	1[1]	2[1]	3[1]	4[1]	5[1]	6[1]	7[1]	8[2]	9[3]	10[3]	11[4]	12[4]	13[4]	14[5]	15[5]	16[5]	17[5]	18[5]	19[6]	20[7]	AVG
Procedure	SM	SM	SM	SM	SM	SM	SM	SM	SM	SM	SM	SM	SM	ASA	ASA	ASA	ASA	ASA	ASA	SM	–
Age (Years)	53	37	44	41	59	72	57	46	54	44	67	56	65	41–54	41–54	41–54	41–54	41–54	53	38	51
Sex	M	F	F	F	F	F	F	M	M	F	M	M	M	M	M	M	M	M	M	M	–
Pre-operative ventricular septal thickness (mm)	42	28	24	23	23	19	23	26	25	35	30	19	31	–	–	–	–	–	22	24	26
Pre-operative LVOT Peak Gradient (mmHg) at rest	100	75	95	174	121	67	81	90	100	74	100	70	120	165	85	170	60	85	126	64	101
Pre-operative LV ejection fraction (%)	76	67	73	63	76	73	69	–	76	–	60	70	65	–	–	–	–	–	–	65	69
Systolic anterior motion of the mitral valve	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	+	+	–
Weight of myocardium removed (grams)	–	–	–	–	–	–	–	4.5	–	–	–	–	–	–	–	–	–	–	–	4.8	4.6
Post-operative LVOT Peak Gradient (mmHg) at rest	6	0	0	18	0	10	13	27	0	5	15	14	0	57	10	6	15	10	57	10	13.6
Minimum follow up time post-op (months)	3	3	3	3	3	3	3	1	5	3	5	5	5	12	12	12	6	6	15	3	5.5
New York Heart Association Class Pre-operatively	3	3	3	3	3	3	3	D	D	D	3	3	3	–	–	–	–	–	3	3	3
New York Heart Association Class Post0operatively	2*	2*	–	1	2	1	1	0	0	0	2	1	1	–	–	–	–	–	1	0	0–1
Pre-operative ERT	+	0	+	0	+	0	+	+	+	+	0	0	0	–	–	–	–	–	0	+	–
Total 12-Lead QRS Voltage (mm)	–	–	–	–	–	–	–	232	–	–	–	–	–	–	–	–	–	–	–	213	222
Leukocyte alpha-galactosidase activity (nmol/hr/mg)	0.2	4.6	18.3	26.8	14.7	14.5	11	–	–	–	–	–	–	–	–	–	–	–	–	0.9	11.37

ASA = alcohol septal ablation; AVG = average; D = dyspnea; F = female; LVOT = left ventricular outflow tract; M = male; SM = surgical myectomy.

* Patient 1 developed progressive cardiac wall thickening and recurrence of NYHA class 3 dyspnea at 6 years. Patient 2 had recurrence of NYHA class 3 symptoms and progression of chronic kidney disease to stage 3 at 3-year follow up. 1-Meghji et al,[7] 2-Blount et al,[8] 3-Kunkala et al,[9] 4- Cecchi et al,[10] 5- Zemanek et al,[11] 6-Magage et al,[12] 7-Present case.

longitudinal strain that is markedly abnormal in the basal inferolateral wall (Figure 3). This finding is not sensitive but can provide a clue to diagnosis when present.[4] CMR is required to confirm the diagnosis of FD cardiomyopathy. Noncontrast myocardial T1 values are reduced in patients with FD due to increased levels of glycosphingolipids in the myocardium. Noncontrast myocardial T1 mapping can distinguish FD from LV hypertrophy due to hypertension, HC, amyloidosis, and aortic stenosis with almost perfect sensitivity and specificity.[2] When imaging is not sufficient endomyocardial biopsy may be pursued to confirm the diagnosis. In the present case, the patient had a characteristic global longitudinal strain pattern on echo and decreased T1 on CMR that confirmed the diagnosis of cardiac FD.

Treatment of FD cardiomyopathy is centered on the use of ERT. ERT is performed with the administration of recombinant alpha galactosidase which decreases the deposition of globotriaocylceramide. Long-term ERT can cause improvements in LV mass and may improve ejection fraction.[5] Limited data is available on the effect of ERT on mortality and hospitalizations. ERT is more effective if started early in the disease course, as patients with preexisting myocardial fibrosis have less benefit. The current patient was treated with ERT for 5 years before presentation but his LV hypertrophy continued to progress and led to the development of severe LV outflow tract obstruction. Despite treatment with β-blockers his symptoms continued to progress and he was referred for surgical myectomy.

The epidemiology and outcomes of FD patients undergoing septal reduction therapy is not known. We undertook a review of the available cases and summarized them in Table 1. Six patients from a single center underwent alcohol septal ablation, all others were treated with surgical myectomy. The average ventricular septal thickness was 26.2 mm and average peak LV outflow tract gradient at rest was 101 mm Hg. Total 12 lead QRS voltage and electrocardiograms were not available in the majority of cases. In the present case and one other case, total 12 lead QRS voltage was 213 and 232, respectively. This is similar to reported mean 12 lead QRS voltage in patients with severe aortic valve stenosis and slightly higher than patients with HC.[6] The average age of patients was 51 years, the patient in this case was aged 38 years and was the youngest patient to undergo surgical myectomy. The weight of myocardium removed was reported only in one other case at 4.5 grams, similar to the 4.8 grams removed in the present case. All patients had significant short-term improvement of LV outflow tract gradient and symptoms (if symptoms were reported). Longer term follow-up has only been reported by Meghji et al. In their cohort of 6 patients, none had reoccurrence of LV outflow tract gradient at 2 years. At 3 and 6 years, 2 patients developed heart failure symptoms due to progressive renal disease and cardiomyopathy from FD.[7] Seven of the cases had been treated with ERT before surgery and still went on to develop significant LV outflow tract obstruction. This reinforces the limitations of ERT therapy. If ERT is not initiated early in the disease course, patients with elevated LV mass and fibrosis show minimal improvement in wall thickness and exercise capacity.[5]

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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