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Short communication

Surgical septal myectomy for relief of dynamic obstruction in Anderson-Fabry Disease

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ABSTRACT

Patients with Anderson-Fabry Disease (AFD) and severe left ventricular hypertrophy complicated by left ventricular outflow tract (LVOT) obstruction may benefit from surgical septal myectomy (SSM). Mid- and late outcomes following surgery have not been established, and we sought to better characterize postoperative outcomes following septal myectomy. Between January 2011 and June 2017, 7 patients (6 females) with AFD underwent SSM. The median (range) age at the time of surgery was 53 (37–72) years; 4 patients had a positive family history of AFD and a preoperative diagnosis of AFD. Extracardiac features suggestive of AFD were present in 3 patients and all but 1 (female) had reduced α-galactosidase A activity. All patients had severe left ventricular hypertrophy and LVOT obstruction on transthoracic echocardiography. Preoperatively, all patients were severely symptomatic with New York Heart Association (NYHA) class III symptoms. There was no early mortality following surgery. The median in-hospital length of stay was 5 (4–7) days with 6 patients reporting NYHA class II or less symptoms at 3 month follow-up. Long-term outcomes were favorable with 4 patients reporting sustained NYHA class II or less symptoms, but 2 patients had recurrence of NYHA class III symptoms without evidence of recurrent LVOT obstruction. In conclusion, SSM appears to provide favorable short- and long-term relief of severe, symptomatic LVOT obstruction but may not alter progression of Fabry cardiomyopathy.

1. Introduction

Anderson-Fabry Disease (AFD) is an X-linked recessive lysosomal storage disorder caused by a deficiency of α-galactosidase A (α-Gal-A) enzyme activity due to mutation in the *GLA* gene [1]. Cardiac involvement in AFD is common and cardiovascular death is an increasingly recognized cause of mortality. Cardiac manifestations of AFD may mimic hypertrophic cardiomyopathy with severe left ventricular hypertrophy, systolic anterior motion of the mitral leaflets, left ventricular outflow tract (LVOT) and/or mid-cavitary obstruction, and apical aneurysms [2–4]. These patients are often symptomatic despite treatment with recombinant α-Gal-A enzyme replacement therapy (ERT), but data on surgical and percutaneous interventions for management of LVOT obstruction in AFD are limited to case reports. The short- and long-term outcomes of patients with AFD undergoing septal myectomy are unclear [5–9]. Thus, we sought to describe the postoperative outcomes among patients with severe left ventricular hypertrophy due to AFD complicated by LVOT obstruction.

2. Methods

The study was approved by the Institutional Review Board at our institution and informed consent was obtained from all participants. From January 2011 to June 2017, 7 patients with AFD underwent surgical septal myectomy (SSM) for symptomatic dynamic LVOT obstruction. Short-term follow-up was based on clinical documentation within 1–3 months of surgery. Short-term clinical outcomes have been previously reported in three of the patients (patients 1, 3 and 5) in this series [5,9]. Patients were contacted to ascertain long-term symptom status and complications.

Transthoracic echocardiographic data were collected according to the American Society of Echocardiography recommendations. The following echocardiographic parameters were abstracted: resting and provoked LVOT and midventricular maximal instantaneous gradient, interventricular septal thickness, posterior wall thickness, and right ventricular systolic pressure.

An extended transaortic septal myectomy was performed in all patients. Histology and electron microscopy findings, when available, were reviewed for all patients. Data were analyzed using JMP, version 13.0 (SAS Institute Inc., Cary, North Carolina). Categorical variables are expressed as counts (percentages) and continuous variables as median (range).

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3. Results

From January 2011 to June 2017, 7 patients (6 females) with AFD underwent SSM at our institution. The median age at the time of surgery was 53 (37–72) years.

Preoperative characteristics of 7 unrelated patients with AFD are shown in Table 1. The diagnosis of AFD was established preoperatively in 4 patients with a family history of AFD. Extracardiac features of AFD (hypohidrosis, angiokeratomas, and acroparesthesia) were present in 3 patients. All but 1 patient (female) had reduced leukocyte α-Gal-A activity with a median value of 14.5 (0.2–26.8) nmol/h/mg (normal reference in our lab: ≫23.1 nmol/h/mg). Of note, the lone female patient with normal α-Gal-A activity had both a family history and a preoperative diagnosis of AFD. Three (43%) patients were on ERT prior to surgery. At the time of surgery, all patients described New York Heart Association (NYHA) class III symptoms and were treated with negative inotropes (beta blocker or disopyramide).

Preoperative transthoracic echocardiography showed severe concentric septal hypertrophy, systolic anterior motion of the mitral leaflets, and LVOT obstruction in all patients with interventricular septal thickness of 23 (19–42) mm, posterior wall thickness of 16 (13–24) mm, resting LVOT maximal instantaneous gradient of 95 (67–174) mm Hg, and right ventricular systolic pressure of 32 (23–66) mm Hg.

All 7 patients had evidence of prominent sarcoplasmic vacuolization on histologic examination of surgical specimens. Electron microscopy was performed in 5 patients and 4 specimens had characteristic myelinoid inclusions (concentric lamellar bodies). Six patients underwent genetic testing. *GLA* mutations are presented in Table 1.

All patients had substantial reduction of resting LVOT gradient to 6 (0–18) mm Hg. Patient 3 had an implantable cardioverter defibrillator placed 3 days postoperatively for primary prevention of sudden cardiac death due to her previous history of non-sustained ventricular tachycardia. Patient 5 had concomitant aortic valve repair and coronary artery bypass grafting. She sustained a transient ischemic attack on postoperative day 3 and recovered completely. There was no early mortality. Median in-hospital length of stay was 5 (4–7) days, with 6 patients reporting NYHA class II or less symptoms at 3 month follow-up. One patient was lost to follow-up.

During a median follow-up of 24 (8–84) months, 3 patients developed atrial fibrillation and 6 patients were receiving ERT. Two patients had recurrence of NYHA class III symptoms (Patients 1 and 2) but no evidence of recurrent LVOT obstruction. Patient 1 had progressive cardiac wall thickening and recurrence of NYHA class III exertional dyspnea at 6 year follow-up. Patient 2 had recurrence of NYHA class III symptoms with a hospitalization for heart failure (NT Pro-BNP 2890 pg/mL) and progression to chronic kidney disease stage III (eGFR = 44 mL/min/1.73 m^2) at 3 year follow-up.

4. Discussion

In this cohort of 7 patients with AFD and severely symptomatic LVOT obstruction, SSM resulted in durable relief of dynamic obstruction with excellent short-term and acceptable long-term clinical outcomes. Surgical complications were limited to one transient ischemic attack with complete recovery in a patient who underwent concomitant aortic valve replacement. Postoperatively, there was a substantial reduction in the maximal instantaneous gradient (Fig. 1) accompanied by marked improvement of exertional symptoms in all patients. On prospective long-term follow-up, there were no recurrences of dynamic obstruction, although 2 patients developed NYHA class III symptoms despite ERT at 3 and 6 years, respectively, due to progression of Fabry cardiomyopathy and progressive kidney disease.

Since 2001, the standard treatment for AFD has been recombinant ERT [10,11]. Yet, many patients with AFD continue to have disease progression on ERT [12–15]. Three patients in our series had progressive exertional symptoms and severe LVOT obstruction despite receiving ERT. This is not surprising since ERT has not been convincingly shown to induce regression of ventricular hypertrophy and does not alleviate dynamic obstruction. When exertional symptoms persist despite ERT, few therapeutic options remain [16]. The role of advanced heart failure therapies (left ventricular assist device, cardiac transplantation) is not

Table 1
Characteristics of seven patients with Anderson Fabry Disease.

Characteristics	Patient no.						
	1	2	3	4	5	6	7
Age at surgery (years)	53	37	44	41	59	72	57
Sex (M: male; F: female)	M	F	F	F	F	F	F
BMI (kg/m^2)	23.5	26	37	30	29.5	24	31
Hypertension	0	0	+	0	+	+	0
Coronary artery disease	+	0	0	0	+	0	0
Preoperative diagnosis of AFD	+	0	+	+	0	0	+
Family history of AFD	+	0	+	+	0	0	+
Preoperative ERT	+	0	+	0	0	0	+
NT-Pro BNP (pg/mL)[a]	3061	4227	1304	7188	-	1244	4525
Leukocyte α-galactosidase A activity (nmol/h/mg)[b]	0.2	4.6	18.3	26.8	14.7	14.5	11
Genotype	G373S	N215S	L303N	-	P409S	N215S	P259L
Preoperative LVOT gradient (mm Hg)	100	75	95	174	121	67	81
Preoperative left ventricular wall thickness (mm)							
Interventricular septum	42	28	24	23	23	19	23
Posterior wall thickness	24	15	19	17	15	16	13
Preoperative left ventricular ejection fraction (%)	76	67	73	63	76	73	69
Postoperative LVOT gradient at rest (mm Hg)	6	0	0	18	0	10	13
Postoperative left ventricular wall thickness (mm)							
Interventricular septum	30	28	26	20	18	17	14
Posterior wall thickness	24	15	15	17	15	15	13
Postoperative left ventricular ejection fraction (%)	78	67	68	75	59	80	73
NYHA class at follow-up	III	III	-	I	II	I	I
Ejection fraction at follow-up (%)	58	75	-	-	-	63	70
NT-Pro BNP (pg/mL)[a] at follow-up	-	2890	-	-	-	1421	-

BMI = Body Mass Index; AFD = Anderson Fabry Disease; ERT = enzyme replacement therapy; LVOT = left ventricular outflow tract; A plus sign (+) indicates presence of a finding, a zero (0) for its absence or negative and a dash sign (-) means no information available.

[a] NT-proBNP values ≪ 300 pg/mL have a 99% negative predictive value for excluding acute congestive heart failure.

[b] Values in normal subjects are ≥23.1 nmol/h/mg.

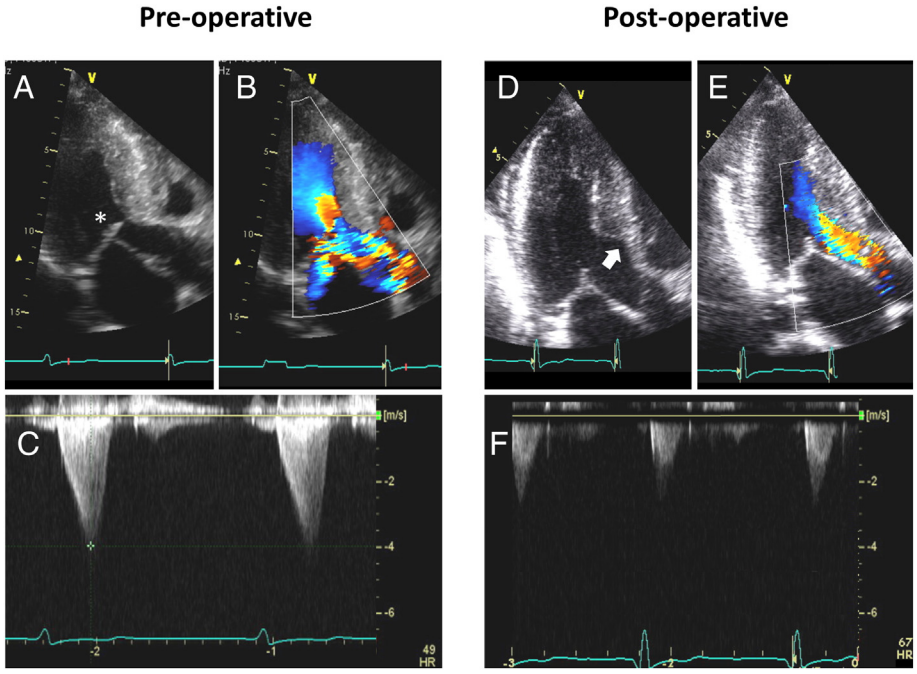

Fig. 1. Pre- and post-operative transthoracic 2D and Doppler echocardiography in a severely symptomatic patient (Patient 3) with Anderson-Fabry Disease following septal myectomy for dynamic LVOT obstruction. A) Apical long axis view demonstrates severe increase in left ventricular wall thickness with asymmetric basal septal hypertrophy and SAM of the mitral apparatus (*). B) Color Doppler reveals aliasing in the LVOT with posteriorly directed (SAM-mediated) mitral regurgitation. C) Continuous wave Doppler recordings from the apical long-axis window revealed a maximal instantaneous gradient of 64 mm Hg. D) The post-operative echocardiogram reveals post-myectomy findings (arrow). E) SAM of the mitral apparatus is no longer present and color aliasing is not identified. F) LVOT dynamic obstruction is no longer present. AFD = Anderson-Fabry Disease; LVOT = left ventricular outflow tract obstruction; SAM = systolic anterior motion.

well established in patients with AFD. In our cohort, surgical myectomy was safe and resulted in immediate relief of exertional dyspnea and LVOT obstruction. In 2 patients with progression of Fabry cardiomyopathy and new symptoms at 3 and 6 years, respectively, both reported high satisfaction with SSM and an absence of symptoms reminiscent of LVOT obstruction.

Cecchi et al. [6] reported on the intraoperative diagnosis of AFD among 3 male patients with left ventricular hypertrophy and clinical suspicion of hypertrophic cardiomyopathy. Following SSM, AFD was confirmed through histological examination and *GLA* testing. In this cohort, 4 patients had a preoperative diagnosis of AFD and 3 patients (patients 2, 5 and 6) were intraoperatively suspected to have intramyocardial storage disorder. The surgical findings included cardiac muscle that was "pale" and "more friable than usual." All 3 males in the study by Cecchi et al. carried the N215S mutation, whereas the lone male in this study carried the G373S mutation and the N215S mutation was the most frequently identified mutation in females. Calcagnino et al. [7] also identified the N215S allele in 4 of 14 patients with AFD and exercised-induced LVOT obstruction. Two female patients proceeded to SSM for refractory symptoms, however, neither the mutation nor the long-term clinical outcomes were reported [7]. Although the specific mutation was not reported, Blount et al. [8] also reported on the successful short-term clinical outcome of SSM in an affected male patient. Taken together, these findings support the consistent observation that SSM is an appropriate treatment strategy and that the N215S allele is the most frequently identified pathogenic *GLA* mutation among AFD patients with severe LVOT obstruction and refractory symptoms.

In conclusion, AFD patients with severe, symptomatic LVOT obstruction refractory to ERT and/or conventional medical treatments present a complex therapeutic dilemma. There are few treatment options in these patients and the role of advanced therapies such as cardiac transplantation and left ventricular assist device are not well established. Although surgical myectomy may not alter the natural history of Fabry cardiomyopathy, it was associated with excellent operative outcomes, long-term resolution of dynamic obstruction, and acceptable symptomatic relief in selected patients.

Conflict of interest

None declared.

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