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Case Report

Septal Myectomy in Patients with Hypertrophic Cardiomyopathy and Non-Classical Anderson-Fabry Disease

Alexandr Gurschenkov ^{1,*}, Sofiya Andreeva ², Vadim Zaytsev ¹, Pavel Khazov ¹, Gleb Ischmukhametov ¹, Alexandra Kozyreva ², Polina Sokolnikova ², Olga Moiseeva ¹, Anna Kostareva ^{2,3,*} and Mikhail Gordeev ¹

¹ Institute of Cardiovascular Science, Almazov National Medical Research Centre, Saint Petersburg, Russia.

² World-Class Research Centre for Personalized Medicine, Almazov National Medical Research Centre, Saint Petersburg, Russia.

³ Department of Woman and Children's health, Karolinska Institutet (KI), Stockholm, Sweden

* Correspondence: anna.kostareva@ki.se

Abstract: Anderson-Fabry disease (AFD) results from decreased enzyme activity of lysosomal enzyme and intralysosomal storage of its nonhydrolyzed. Cardiovascular complications, mainly in the form of HCM contribute substantially for AFD-patient's mortality. Here we report three new cases of obstructive HCM (HOCM) due to unclassical presentation of AFD and isolated cardiac involvement. In all three cases the diagnosis of AFD was made postoperative by routine genetic and morphological testing. Together with previously published cases this report illustrates the potential safely and beneficial effect of septal surgical myectomy in patients with AFD-HOCM, as well as underlines the need for more thorough screening for clinical signs of AFD-associated cardiomyopathy and *GLA* variants among patients with HOCM.

Keywords: hypertrophic cardiomyopathy; obstructive; myectomy; Anderson-Fabry disease; *GLA*

1. Introduction

GLA gene encodes for α -galactosidase enzyme and its over 850 pathogenic and likely pathogenic variants are all associated with the only clinical phenotype - Anderson-Fabry disease (AFD). This disease results from decreased enzyme activity and intralysosomal storage of its nonhydrolyzed substrate – globotriaosylceramide [1,1]. The most suffering cells and tissues are heart, kidney and nervous system, as well as eyes and ears due to endothelial damage and intracellular storage of undegraded substrates [2]. The classical form of the disease progress permanently leading to substantial decrease of quality of life and life expectancy [3]. Cardiovascular complications contribute substantially for AFD-patient's mortality and since one half of the patients without left ventricular hypertrophy develop it within 15 years [4]. Apart from classical form with typical presentation and systemic organ damage there have been described non-classical and non-penetrant forms with late manifestation and isolated organ involvement – mainly cardiovascular system or kidney. These cases constitute a substantial diagnostic challenge often leaving the patient without correct clinical and genetically proved diagnoses, enzyme replacement therapy or proper estimation of risk factors. Thus, despite the fact that hypertrophic cardiomyopathy is a well-known cardiovascular presentation of Fabry disease in a form of subaortic, midventricular or apical hypertrophic remodeling, there are only several reports on obstructive form of AFD-HCM demanding surgical septal myectomy (SSM) [5–12]. In most of the cases the patients reported were admitted to surgical treatment with already established diagnosis of AFD and only in few cases the patients were treated as having classical HCM and the precise diagnosis became obvious only after cardiac surgery. Here we report three new cases of obstructive HCM due to unclassical presentation of AFD and isolated cardiac involvement. In all three cases the diagnosis of AFD was made postoperative by routine genetic and morphological testing. In addition, we summarize all previously published cases of SSM in patients with AFD giving

the summary on a safety and benign prognosis of such operations in patients with AFD. Our series in addition to previously reported underlines the safety and effectiveness of SSM in obstructive form of AFD.

2. Case Reports

Three patients were enrolled in Almazov National Medical Research Centre during 2016-2022 to perform SSM due to obstructive form of HCM without previously known diagnosis of ADF disease. The main clinical characteristics of patients are summarized in Table 1. In all patients, standard clinical examination including echocardiography and Holter ECG monitoring were performed prior to cardiac surgery. MRI images were obtained using ultra-high field tomography Magnetom Trio A Tim 3,0 T₁ (Siemens) with 8 mm slices using Gd-DO3A 0,2 ml/kg contrasting. Of note, two out of three patients underwent non-ST MI prior to operation and one of them had classical angina without any intracoronary obstruction according to angiography. In one patient a pacemaker was implanted due to II-degree AV-block (type 2). Nobody of the patients revealed ventricular tachycardia, while all three presented with premature ventricular contractions grade III-IV Ryan. All patients revealed various degree of myocardial fibrosis according to MRI either in both ventricles (Patient 1), in IVS and LV (Patient 2) or solely in left ventricle (Patient 3). Only Patient 1 had increased right ventricular thickness. All surgical procedures were performed with cardiac arrest under retrograde Calafiore blood cardioplegia according to B. Messmer modification [13]. In one case (Patient 1) vena cava superior was dissected in order to verticalize interventricular septum due to poor visualisation. In Patient 3 mitral second-order chordae resection of anterior mitral valve leaflet was performed [14]. All three patients had no postsurgical complications and were discharged at day 14-16 with remarkable clinical and subjective improvement (CHF class I-II and no signs of angina). Morphological examination confirmed extensive fibrosis and disarray.

Table 1. Clinical characteristics of HOCM patients before myectomy.

Clinical parameter	Patient 1	Patient 2	Patient 3
sex	male	female	female
Age at diagnosis of HOCM	51	69	58
Hight/Weight/BMI	174/66/21,8	162/90/34,3	182/96/29
Genetic variant, hg19	chrX:100653857T>C, c.717A>G, Ile239Met; NM_000169.3; rs1928192530	chrX:100656740C>T, c.427G>A, Ala143Thr NM_000169.2; rs104894845	chrX:100654790T>C c.640-856A>G; NM_000169.3
α-GAL A activity on leucocytes, nmol/mL/h	-	5,46	-
Plasma LysoGb3 level	-	0,43	0,78
NYHA at first evaluation	III	III	III
AF	+	-	-
Angina	+	-	-
MI in anamnesis	+ (non-ST)	+ (non-ST)	-
Coronary artery obstruction	-	-	-
Pacemaker	-	+	-
Kidney involvement	+	+	-
Angiokeratomas	-	-	-
Neurological symptoms	-	-	-

LysoGb3 - globotriaosylsphingosine; AF — atrial fibrillation; MI — myocardial infarction; SSC – surgical.

All patients were alive 12 and 18 month postoperatively and remained on CHF II (Patients 1 and 2) and class I (Patient 3). Of note, in all three patients CHF symptoms along with elevated NT-proBNP level persisted one year after surgery despite a marked reduction of LVOT gradient. In addition, none of the patient demonstrated clinically marked PVC and or had indications for ICD implantation in spite of severe LVOD gradient before surgery.

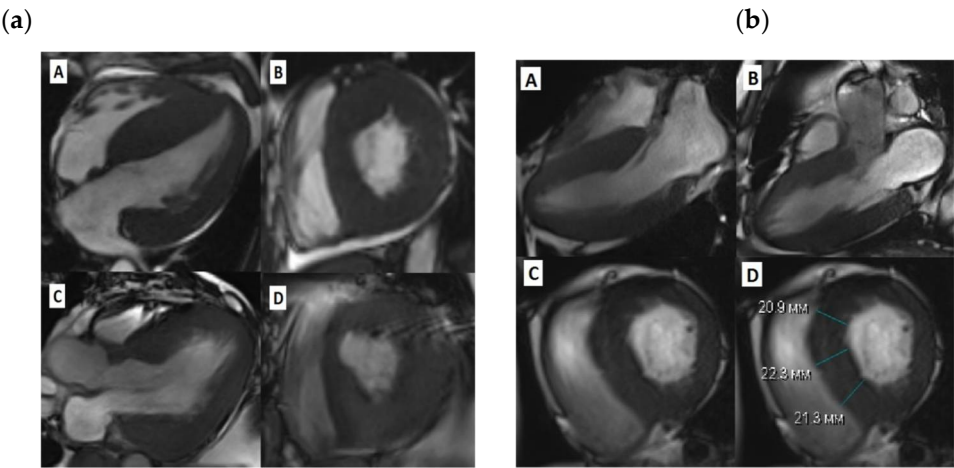


Figure 1. Cardiac MRI before and after SSM. (a)-Patient 1, A-diastolic view before SSM, long LV axis, B- diastolic view before SSM, short LV axis, C -diastolic view after SSM, long LV axis, D-diastolic view after SSM, short LV axis; **(b)-Patient 3,** A, B-diastolic view before SSM, long LV axis, C,D - diastolic view before SSM, short LV axis;.

Table 2. Echocardiographic data of HOCM patients before myectomy.

Clinical parameter	Case 1	Case 2	Case 3
IVS mm	32	25	17
LVPW (d) mm	26	16	12
LVOT max gradient, mmHg.	112	130	110
LA mm	52		
LV EF %	74	78	73
RVW (d) mm	9	5	4
TAPSE	22	21	20
SAM + \ -	+	+	+
MR	0	I – II	II – III

MR – mitral regurgitation, SAM – systolic anteriur motion of mitral valve, RVW(d) right ventricular wall (diastolic dimation), LV EF – left ventricular ejection fraction, LVPW (d) left ventrycular posterior wall (diastolic dimation), IVS – interventricular septum.

Table 3. Intraoperative characteristic of patients with HOCM during SSM.

Intraoperative characteristics	Patient 1	Patient 2	Patient 3
Type of surgery	Extended myectomy	Extended myectomy	Extended myectomy+MV plastic
Time of circulatory arrest (min)	70	62	60
Time of aorta clip (min)	43	55	49
Excised myocardial mass (gr)	6,37	8,1	3,41
IVS thickness at subaortic level (mm)	16	16	10
LV maximum thickness (mm)	31	16	15

Maximum LVOT gradient	30	12,9	11,9
LV EF % at day 7 postoperatively	71	69	63
MR*	0	I	0

MV – mitral valve IVS – interventricular septum; LV – left ventricle; LVOT – left ventricular outflow tract; LV EF – left ventricular ejection fraction; MH – митральная недостаточность.

3. Discussion

In spite of a well-known fact that AFD often manifests with cardiac phenotype in a form of HCM, the diagnostic work up in case with atypical AFD with only cardiovascular symptoms remains a challenge. Importantly, since the use of HCM risk calculator is not validated for patients with storage diseases, no straightforward clinical guidelines for ICD implantation can be used in patients with identified *GLA* mutations. The same is valid for other treatment strategies of HCM in case of metabolic and storage disorders. This group of patients drops off the current guidelines and treatment algorithms since these patients fully manifests neither classical signs of AFD phenotype no HCM clinical cause. For this reason, a newly proposed staging for AFD-associated HCM was recently offered to better define the treatment strategy, surgical risks and patient’s prognosis [15]. Currently, AFD contributes for only small proportion of HCM, approximately 0.4-1% [11,16]. However, with implementation of routine genetic testing in HCM diagnostics the number of reported patients with non-classical AFD among HCM patients is constantly increasing including a group of surgically treated patients. Thus, among patients with HOCM AFD is reported to contribute to 0,5-2% [10]. Several interventional and surgical options can be offered to patients with HOCM including myectomy and septal alcohol ablation [17]. Myectomy also aims on reducing LVOT gradient, relieving the exercise intolerance and improving HF symptoms in patients with LVOT obstruction. Of note, in growing number of cases the defined diagnosis of AFD is established only during surgical operation due to operators attention to the myocardial tissue structure, meaning that a number of patients with HOCM do not have any red flags of AFD prior to surgery [9]. However, storage disorders are often considered as an untarget group for myectomy since no systematic data, review or metanalysis are performed on the effectiveness of surgical treatment and the cause of postoperative period in this group of patients.

Several case reports have been described on patients with AFD performed surgical myectomy. Together with 3 patients presented in this study overall 22 patients who underwent open surgery treatment due to HOCM and AFD are reported by now (Table 4). In almost half of the cases the diagnosis of AFD was established prior to surgery and 9 out of 22 patients obtained enzyme replacement therapy.

Table 4. Cases of HOCM due to AFD underwent SSM.

	Diagnosis established before surgery	Age at the moment of myectomy	Sex	Non-cardiac manifestations	ERT	LVOT gradient	Post-surgery complications	Successful discharge	Reference
1	+	53	m	+	+	100	-	+	Meghji [5]
2	-	37	f	-	-	75	-	+	
3	+	44	f	+	+	95	-	+	
4	+	41	f	+	-	174	-	+	
5	-	59	f	-	-	121	+	+	
6	-	72	f	-	-	67	-	+	
7	+	57	f	+	+	81	-	+	
8	+	56	f	+	+	152	-	+	Calcagnino [12]
9	+	n/a	f	+	+	56/58	-	+	
10	-	59	m	-	-	100	+	+	Frustachi [10]
							(LV disfunction, acute kidney injury)		
11	-	67	m	-	-	100	-	+	Cecchi [9]
12	-	56	m	-	-	70	-	+	
13	-	65	m	-	-	120	+	+	
							(VT)		
14	+	54	m	+	+	100	-	+	Kunkola [6]

15	+	44	f	-	+	95	-	+	
16	+	38	m	+	+	190	-	+	Raju [7]
17	+	55	n/a	-	-	85	+	+	Xiao [11]
18	+	49	n/a	+	-	88	-	+	
19	+	46	m	-	+	90	-	+	Blount [8]
20	-	51	m	+	-	112	-	+	Current study
21	-	69	f	+	-	130	-	+	
22	-	58	f	-	-	110	-	+	

LV – left ventricle, EF – ejection fraction, ERT- enzyme replacement therapy, AFD- Anderson-Faby disease, HOCM-hypertrophic obstructive cardiomyopathy, SSM-surgical septal myectomy.

Importantly, despite of the well documented effect of ERT for patients with AFD in terms of the organ damage and disease progression [18], its protective effect on progression of cardiomyopathy and relieving HF symptoms is not obvious [19,20]. One of the explanations can be related to the possible immune and cell-stress-mediated mechanisms of cardiomyocyte injury and hypertrophy in AFD-cardiomyopathy, which are, once being induced, can undulate long time in spite of the absence of initial metabolic alterations and effective ERT [19,21]. This notion can be supported by the fact that 9 out of 22 patients underwent myectomy had ERT and, however, reached the indication for surgical treatment due to progression of hypertrophy and obstruction. Data exists regarding the most beneficial effect of ERT or chaperon therapy with megalostat on cardiac function in patients with very early stage of cardiac involvement and the decreased effect of specific therapy on cardiac function in patient with advanced cardiomyopathy and hypertrophy [19,21,22]. Importantly, the molecular mechanism of cardaiac-only AFD can be slightly different from the cases with full disease penetrance and classical presentations. This probably is associated with a defined genetic alteration and the functional effect of the variant of enzyme activity and function. Thus, Ala143Thr variant described in this study has been widely debated as a causative for full-penetrant phenotype of AFD and is demonstrated to be associated with only latte onset cardiomyopathy with incomplete penetrance [23]. Similar is valid for the genetic variant which lead to formation of cryptic splice site and inclusion of addition exones [24]. These low penetrant GAL variants and variants in non-coding regions which are not always covered by target gene panels have to be considered in patients with HOCM as a possible cause of AFD-cardiac only phenotype.

5. Conclusions

In conclusion, we described three new cases of successful SSM in patients with HOCM due to AFD. In all three patients the genetic diagnosis was established only after surgical procedure since patients did not have other classical symptoms of AFD. Together with previously published cases this report illustrates the potential safely and beneficial effect of SSM in patients with AFD-HOCM, as well as underlines the need for more thorough screening for clinical signs of AFD-associated cardiomyopathy and GLA variants among patients with HOCM.

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