Intraoperative Diagnosis of Anderson-Fabry Disease in Patients With Obstructive Hypertrophic Cardiomyopathy Undergoing Surgical Myectomy

Franco Cecchi, MD; Maria Iascone, MD; Niccolò Maurizi, MD; Laura Pezzoli, BSc; Irene Binaco, MD; Elena Biagini, MD; Maria Laura Fibbi, MD; Iacopo Olivotto, MD; Federico Pieruzzi, MD; Ana Fruntelată, MD; Lucian Dorobantu, MD; Claudio Rapesti, MD; Paolo Ferrazzi, MD

IMPORTANCE Diagnostic screening for Anderson-Fabry cardiomyopathy (AFC) is performed in the presence of specific clinical red flags in patients with hypertrophic cardiomyopathy (HCM) older than 25 years. However, left ventricular outflow tract obstruction (LVOTO) has been traditionally considered an exclusion criteria for AFC.

OBJECTIVE To examine a series of patients diagnosed with HCM and severe basal LVOTO undergoing myectomy in whom the diagnosis of AFC was suspected by the cardiac surgeon intraoperatively and confirmed by histological and genetic examinations.

DESIGN, SETTING, AND PARTICIPANTS This retrospective analysis of patients undergoing surgical septal reduction strategies was conducted in 3 European tertiary referral centers for HCM. Patients with a clinical diagnosis of obstructive HCM referred for surgical management of LVOTO were observed for at least 18 months after the procedure (mean [SD] follow-up, 33 [14] months).

RESULTS From 2013, 235 consecutive patients with a clinical diagnosis of HCM underwent septal myectomy. The cardiac surgeon suspected a storage disease in 3 patients (1.3%) while inspecting their heart samples extracted from myectomy. The mean (SD) age at diagnosis for these 3 patients was 42 (4) years; all were male. None of the 3 patients presented with extracardiac features suggestive of AFC. All patients showed asymmetrical left ventricular hypertrophy, with maximal left ventricular thickness in the basal septum (19-31 mm), severe basal LVOTO (70-120 mm Hg), and left atrial dilatation (44-57 mm). Only 1 patient presented with late gadolinium enhancement on cardiovascular magnetic resonance at the right ventricle insertion site. The mean (SD) age at surgical procedure was 63 (5) years. On tactile sensation, the surgeon felt a spongy consistency of the surgical samples, different from the usual stony-elastic consistency typical of classic HCM, and this prompted histological examinations. Histology showed evidence of intracellular storage, and genetic analysis confirmed a GLA A gene mutation (p.Asn215Ser) in all 3 patients.

CONCLUSIONS AND RELEVANCE Screening for AFC should be performed even in the absence of red flags in patients with HCM older than 25 years.
Anderson-Fabry disease (AFD) is an X-linked lysosomal storage disease, characterized by decreased or absent activity of lysosomal α-galactosidase A due to a pathogenic mutation in the α-galactosidase A gene (GLA). As a result of α-galactosidase A deficiency, globotriaosylceramide (GL-3) and other glycosphingolipids are stored in various tissues, including kidney, heart, and skin tissues. The diagnosis of AFD is challenging and often delayed up to 20 years following the onset of symptoms. About 70% of patients with AFD show heart involvement, including left ventricular hypertrophy (LVH), that may be severe and mimic hypertrophic cardiomyopathy (HCM). Anderson-Fabry cardiomyopathy (AFC) is common in male patients with the specific late-onset cardiomyopathy (HCM). Anderson-Fabry cardiomyopathy (AFC) is common in male patients with the specific late-onset cardiomyopathy (HCM). Anderson-Fabry cardiomyopathy (AFC) is common in male patients with the specific late-onset cardiomyopathy (HCM). Anderson-Fabry cardiomyopathy (AFC) is common in male patients with the specific late-onset cardiomyopathy (HCM). Anderson-Fabry cardiomyopathy (AFC) is common in male patients with the specific late-onset cardiomyopathy (HCM). Anderson-Fabry cardiomyopathy (AFC) is common in male patients with the specific late-onset cardiomyopathy (HCM). 

Methods

Study Population
From July 2013 to December 2016, 235 consecutive patients with a clinical diagnosis of obstructive HCM underwent SM in Policlinico di Monza, Monza, Italy, and Spitalul Hospital Monza, Bucharest, Romania, by the same senior surgeon (P.F.). In 3 patients (1.2%), the cardiac surgeon suspected a storage disease while inspecting the heart samples extracted from myectomy. The diagnosis of HCM was based on current 2014 European Society of Cardiology guidelines. Specific cardiac diagnostic red flags for HCM phenocopies were evaluated in all patients, including specific signs of AFC, such as short P-R interval or heart block, concentric LVH and right ventricular hypertrophy, or late gadolinium enhancement (LGE) on the basal posterolateral LV wall on cardiovascular magnetic resonance.

Surgical Management
Patients were preoperatively evaluated and managed following standard of care. Extended transaortic SM was performed with 2 longitudinal incisions in the basal septum 2 to 3 millimeters below the aortic valve and extended distally to the point of mitral septal contact, as previously described.

Histological Examinations and Genetic study
Myocardial samples collected during the surgery were examined by light microscopy following standard procedures. All patients gave informed consent for genetic analysis, which was focused on sarcomere genes associated with HCM and HCM phenocopies (PRKAG2, LAMP2, GLA, TTR, and RASopathies-related genes). 

Key Points

Question Is basal left ventricular outflow tract obstruction an exclusion criterion for Anderson-Fabry cardiomyopathy?

Findings In this case series of 3 patients with hypertrophic cardiomyopathy, we found that Anderson-Fabry cardiomyopathy may mimic hypertrophic cardiomyopathy and present with severely symptomatic left ventricular outflow tract obstruction. The diagnosis was suspected by the cardiac surgeon and confirmed by histological and genetic examinations.

Meaning Screening for Anderson-Fabry cardiomyopathy should be performed even in the absence of red flags in patients with hypertrophic cardiomyopathy older than 25 years.

Results

Baseline Characteristics
The mean (SD) age at HCM diagnosis was 42 (4) years; all were male. None of the 3 patients presented with extracardiac features suggestive of AFD. Patient I was diagnosed after being resuscitated from cardiac arrest, with subsequent implantable cardioverter defibrillator implantation. He had no family history of sudden cardiac death, but his oldest brother previously received a clinical diagnosis of nonobstructive HCM (Figure 1). Patient II was diagnosed after syncope on exertion; family screening showed mildly obstructive HCM in the mother (aged 76 years). Patient III was diagnosed with HCM during routine evaluation for hypertension (Figure 1). All patients reported dyspnea and angina, and both patients II and III had a history of syncope. All were in sinus rhythm at surgery, but patients I and II had a history of paroxysmal atrial fibrillation. All patients showed diffuse and asymmetrical LVH, with maximal LV thickness in the basal septum (19-31 mm), severe basal LVOT gradients (70-120 mm Hg), and left atrial dilatation (44-57 mm) (Table) (Figure 2).
Patient III showed LGE involving the right ventricular insertion site on cardiovascular magnetic resonance. No patients presented with sinus bradycardia, electrocardiographic features suggestive of AFC, or posterolateral LGE on cardiovascular magnetic resonance.

Table. Preoperative and Postoperative Clinical and Echocardiographic Characteristics of the 3 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient I</th>
<th>Patient II</th>
<th>Patient III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Op</td>
<td>Post-Op</td>
<td>Pre-Op</td>
<td>Post-Op</td>
</tr>
<tr>
<td>Age at myectomy, y</td>
<td>67</td>
<td>NA</td>
<td>56</td>
</tr>
<tr>
<td>NYHA class</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>P-R interval &gt;200 ms</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bundle-branch block</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Positive Sokolov-Lyon criteria for LVH</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>History of CAD</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Aborted cardiac arrest</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ICD</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>60</td>
<td>52</td>
<td>70</td>
</tr>
<tr>
<td>Left atrial dimension, mm</td>
<td>57</td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>48</td>
<td>58</td>
<td>41</td>
</tr>
<tr>
<td>IVS thickness, mm</td>
<td>30</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>15</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Basal LVOT gradient, mm Hg</td>
<td>100</td>
<td>15</td>
<td>70</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Mild-moderate</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Abbreviations: CAD, coronary artery disease; ICD, implantable cardioverter defibrillator; IVS, interventricular septum; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NA, not applicable; NYHA, New York Heart Association; post-op, postoperative; pre-op, preoperative; VT, ventricular tachycardia.</td>
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</table>

Figure 2. Preoperative Echocardiographic Parameters and Postmyectomy Specimen

A. Doppler echocardiography of left ventricular outflow tract gradient in patient III. B. Short-axis Doppler echocardiography of left ventricular outflow tract gradient in patient III. C. Hematoxylin-eosin stain sample from patient I. Vacuolization of myocardial tissue is evident and constitutes a typical light microscopy marker of intracellular storage. D. Anteroposterior view of the excised cardiac muscle specimen from patient III (16.7 g), which shows a yellowish instead of the usual reddish color. The cardiac muscle was excised via 2 incisions in the basal septum from 2 to 3 millimeters below the aortic valve and extended distally to the base of the papillary muscles, creating a trapezoid trough that was wider toward the left ventricular apex than at the subaortic level.
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Surgical Procedures

The mean (SD) age at the time of surgery was 63 (5) years. Mean (SD) resection samples weighed 9.6 (5.2) g and were yellowish in color (Figure 2D). On tactile sensation, the surgeon felt a spongy consistency of the surgical samples, different from the usual stony-elastic feel typical of classic HCM, and this prompted histological examinations. The immediate postoperative course was uneventful for patients I and II. Patient III experienced 2 self-terminating episodes of atrial fibrillation and 2 runs of nonsustained ventricular tachycardia. Mean (SD) septal thickness after surgery was 19 (3) millimeters compared with 27 (5) millimeters before surgery (Table).

Histology and Genetic Analysis

Histological examinations showed evidence of intracellular storage with prominent cytoplasmatic vacuolization of the myocytes in all patients. Genetic analysis showed the cardiac AFD variant GLA A gene mutation p.Asn215Ser in all 3 patients (Figure 1). In addition, patient I also had an MYBPC3 variant of unknown significance (p.Arg733Leu), which did not segregate into the family.

Clinical and Hemodynamic Benefit

All patients experienced substantial symptomatic and hemodynamic improvement after surgery (Table). At a mean (SD) postoperative follow-up of 33 (14) months, the outcome was excellent, with patients II and III reporting complete abolition of symptoms, and patient I improving to New York Heart Association class II. The peak basal LVOT gradient was reduced from a mean (SD) of 97 (20) mm Hg before surgery to 10 (7) mm Hg after surgery. No ventricular arrhythmias occurred, and only 1 episode of atrial fibrillation requiring electrical cardioversion was experienced by patient I. Patients I and II refused enzyme replacement therapy, whereas patient III has been treated with α-galactosidase for 10 months, unassociated with further reduction in LVH.

Discussion

The diagnosis of AFD represents an important clinical challenge for the physician because of the heterogeneity of phenotypic manifestations. Anderson-Fabry cardiomyopathy has been reported in 0.5% to 2% of adult patients with HCM but has not yet been recognized as a differential diagnosis in patients with severe resting LVOTO. Genetic analysis should be routinely performed in patients with HCM, even in the absence of any cardiac and extracardiac red flags. Specific genetic screening for AFD, as part of contemporary next-generation sequencing panels for HCM should always include GLA, TTR, PRKAG2, LAMP2, and all potential phenocopies genes, including RASopathies. Indeed, sarcomeric gene mutations of unknown significance are common and may be misdiagnosed when incomplete gene panels are tested, as would have been the case in patient I had GLA not been tested.

Conclusions

In this consecutive surgical series, AFC prevalence was 1.2%. Features that are often—and erroneously—considered to exclude AFC, such as asymmetric LVH and resting LVOTO, may indeed be part of its phenotypic spectrum. Here, the diagnosis was suspected by the cardiac surgeon and confirmed by histological and genetic examinations. Thus, genetic screening for AFC, as part of contemporary next-generation sequencing panels including other rare HCM mimics, should be routinely performed in patients with HCM, even in the absence of cardiac and noncardiac red flags for AFC.
Author Contributions: Dr Cecchi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cecchi, Iascone, Maurizi, Binaco, Fibbi, Olivotto, Rapezzi, Ferrazzi.

Acquisition, analysis, or interpretation of data: Cecchi, Iascone, Maurizi, Pezzoli, Binaco, Biagini, Pieruzzi, Fruntelata, Dorobantu, Rapezzi.

Drafting of the manuscript: Cecchi, Iascone, Maurizi, Pezzoli, Dorobantu.

Critical revision of the manuscript for important intellectual content: Cecchi, Iascone, Maurizi, Binaco, Biagini, Fibbi, Olivotto, Pieruzzi, Fruntelata, Rapezzi, Ferrazzi.

Statistical analysis: Maurizi.

Administrative, technical, or material support: Pezzoli, Binaco, Olivotto.

Supervision: Cecchi, Binaco, Biagini, Olivotto, Pieruzzi, Fruntelata, Dorobantu, Rapezzi.

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REFERENCES


