Late-onset Fabry disease revealed by ventricular tachycardia: A case report

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Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder due to mutations in the GLA gene leading to deficiency of lysosomal α-galactosidase A (α-Gal A). Classic FD causes multiorgan failure, whereas the later-onset phenotype is characterized by predominantly cardiac manifestations. Ventricular arrhythmias are among the complications.1,2

Here, we describe a patient that was referred to our unit for ventricular tachycardia (VT) ablation after suspected myocarditis. Reviewing the case file and a genetic test led us to the diagnosis of atypical FD. Cardiologists and electrophysiologists should be aware of this disease, which is most likely underdiagnosed.

Case report

A 56-year-old man was admitted to the emergency room of our hospital in January 2018. He had experienced a first episode of typical syncope. He had no medical record and no particular family history.

A 12-lead electrocardiogram (ECG), recorded on admission, showed sinus rhythm, with a Q wave in D1 and aVL derivations (Figure 1A). Troponin was initially 240 ng/L, with a peak at 295 ng/L (normal <34 ng/L).

Transthoracic echocardiography (TTE) revealed a left ventricular ejection fraction (LVEF) of 35%–40% with hypokinesia of the inferolateral ventricular wall. Coronary angiography was normal. Cardiac magnetic resonance (CMR) imaging was performed. Cardiac volumes were normal. The end-diastolic thickness of the left ventricular wall was interpreted normal at the septum, and it was thinned to 3 mm at the lateral wall. Late gadolinium enhancement (LGE) showed a diffuse, transmural, subepicardial fibrosis of the lateral wall (Figure 2). The LVEF was estimated at 43%.

The patient was diagnosed with myocarditis. No rhythmic abnormality was observed with continuous ECG monitoring during hospitalization. No electrophysiology study was performed at this time. After 5 days, the patient was discharged home with a prescription of bisoprolol and ramipril.

A CMR was performed 3 months later. It showed the same abnormalities previously described and an LVEF of 48%. No event occurred during 3 months of follow-up.

Three weeks later, the patient was admitted to the emergency room of our hospital for incessant tachycardia. A 12-lead ECG showed monomorphic VT of 220 beats per minute, with QRS morphology of right bundle branch block morphology and inferior axis (Figure 1B). The VT was incessant and poorly tolerated; it required multiple electrical

KEY TEACHING POINTS

- Late-onset Fabry disease is a cause of ventricular tachycardia in adult patients.
- Unexplained left ventricular hypertrophy, inferolateral wall abnormalities, and absence of extracardiac manifestations is the common presentation.
- Measurement of alpha-galactosidase A activity and genetic testing are the key to diagnosis.
- Catheter ablation is a feasible option in case of recurrent ventricular tachycardia.
- Early diagnosis allows initiation of specific therapy and improves clinical outcomes.

KEYWORDS Fabry disease; Ventricular tachycardia; Catheter ablation; Hypertrophic cardiomyopathy; Genetic; Syncope

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cardioversions and treatment with amiodarone, esmolol, and propofol.

After reduction, we performed an electrophysiology study with endocardial mapping under general anesthesia. A Pentaray catheter ( Biosense Webster, Diamond Bar, CA) was inserted in the left ventricle for electroanatomic mapping with CARTO software ( Biosense Webster). No pathologic substrate was found and no tachycardia was inducible. We ended the procedure without ablation. Finally, this electrical storm was stabilized with medical treatment. A dual-chamber implantable cardioverter-defibrillator (ICD) was placed for the secondary prevention of sudden cardiac death (SCD).

During the follow-up, the patient had several recurrences of VT successfully treated by the ICD. He was referred to our department for another ablation procedure with an epicardial approach in September 2018. Epicardial bipolar voltage mapping showed scar areas located on the inferolateral wall and apex of the left ventricle. Delayed and fragmented electrograms were observed and annotated (Figure 3A). The clinical VT was induced by stimulation, with an identical cycle length of 260 ms and same QRS morphology. Activation mapping was not possible owing to poor hemodynamic tolerance. Pace mapping suggested a potential exit point of a VT isthmus in a border zone, with a best matching of 76% near a poor matching of 56% (Figure 3B). Before ablation, left

Figure 1  Electrocardiogram (ECG) of the patient. A: A 12-lead ECG, recorded on first admission, shows the patient in sinus rhythm. B: A 12-lead ECG shows the patient in ventricular tachycardia.
Phrenic nerve course was tagged using pacing. We performed substrate-based ablation with radiofrequency (SmartTouch catheter; Biosense Webster), aiming at the elimination of all local abnormal ventricular activities. Tachycardia was no longer inducible at the end of the procedure. No phrenic nerve injury occurred. Amiodarone was stopped after the procedure, and the patient continued treatment with bisoprolol and ramipril.

Owing to the atypical evolution for suspected myocarditis, a large genetic screening for hereditary cardiomyopathy was performed. This molecular approach allowed us to detect the presence of a hemizygous pathogenic variant on exon 5 of GLA gene: p.Ser238Asn (NM_000169.2(GLA):c.713G>A). According to this result, FD was highly suspected.

Plasma α-Gal A activity was severely decreased to 0.30 μmol/L/h (normal range: 2.66–10.20 μmol/L/h). Plasma lyso-globotriaosylceramide (lyso-Gb3) was elevated to 14.7 nmol/L (normal <0.6 nmol/L). These findings confirmed the diagnosis of FD, 8 months after the initial syncope.

We found no extracardiac signs of FD. In particular, renal function was normal and brain magnetic resonance imaging showed no sign of FD. There were no other cases of FD found among the relatives. The patient has only male children, so cascade family genetic testing was not performed. The patient was treated with migalastat (Amicus Therapeutics, Philadelphia, PA), an oral chaperone therapy.

A 36-month follow-up with telecardiology did not reveal any recurrence of VT. There is no sign of heart failure and TTE shows a stable LVEF around 50%.

**Discussion**

FD is an X-linked lysosomal α-Gal A deficiency that causes multisystemic disorders, in its classical form. It is more common in males, but females can also be affected. Patients with the later-onset phenotype are probably underdiagnosed. FD has been reported with a prevalence of 1% in a population of hypertrophic cardiomyopathy. Cardiovascular complications are the leading cause of mortality. Cardiologists and electrophysiologists might encounter a patient with unknown FD and should be aware of some warning signs.

The most common cardiac manifestation is progressive left ventricular hypertrophy (LVH). LVH can be severe and mimic hypertrophic cardiomyopathy. In this case study, the left ventricular septum thickness was initially interpreted as normal on CMR. TTE evaluated it between 13 and 15 mm, depending on the exams. These findings could have been considered an indication for an earlier measurement of α-Gal A activity, according to current European guidelines on the diagnosis and management of hypertrophic cardiomyopathy. After the results of genetic testing, a review of CMR evaluated left ventricular septum thickness at 16 mm, which should not have been considered normal.

Inferolateral wall motion abnormalities, particularly basal, are frequently observed in cardiac FD. LGE is typically seen in the basal inferolateral wall in a midmyocardial or subepicardial pattern. This is particularly important, and it has been missed by many physicians. Reduction of inferolateral wall global longitudinal strain is also a sign for the diagnosis.

An ECG with a short PR interval and electrical signs of LVH is another potential indication of cardiac involvement in FD. However, these signs were not observed in our patient. Moreover, sinus node dysfunction and atrioventricular blocks may occur in cardiac FD. Monomorphic VT is also part of the cardiac FD manifestations.

Extracardiac manifestations that should raise suspicion for FD include neuropathic pain, hypohidrosis, angiokeratomas, cornea verticillata, chronic renal failure, proteinuria, stroke or transitory ischemic attack, and gastrointestinal disturbances. These signs are often missing in patients with the later-onset phenotype, which increases the difficulty of a diagnosis.
Our patient was initially diagnosed with myocarditis, because of elevated troponin. This diagnosis should be challenged, particularly in the absence of endomyocardial biopsy, because it can delay the diagnosis of an underlying cardiomyopathy. In our patient, high troponin elevation was probably caused by VT. During chronic follow-up, there was persistent troponin elevation between 70 and 100 ng/L. This finding is related to a direct cardiac injury.

In this case study, a systematic genetic screen with a panel that included GLA led to the correct diagnosis. FD was confirmed by measuring plasma α-Gal A activity. These results showed that genetic testing can facilitate the correct diagnosis of an unclear cardiac disease, even when there is no family history.

In male patients, FD is usually diagnosed by measuring a reduction in α-Gal A activity. A mutation analysis is necessary to establish the disease phenotype and test at-risk family members. In female patients, only a mutation analysis can reveal the diagnosis because measurement of α-Gal A activity is frequently inconclusive.

Diagnosis of FD is of major importance because there are specific treatments that can stabilize or even reverse the organ damage. These treatments are more efficient when initiated early, hence the importance of screening of relatives.

In this study, ventricular arrhythmia was the first manifestation of FD, and the initial syncope was probably caused by VT. In a recent review on ventricular arrhythmias and SCD in FD, 62% of all deaths were reported as SCD and the average prevalence of VT was 15.3%. Identified factors of SCD were age, male sex, LVH, LGE on CMR, and nonsustained VT. Ventricular arrhythmias are frequent in FD with cardiac involvement and patients should be monitored using repeated Holter recordings.

This case study showed that substrate ablation was a successful option on this evolutive disease. We were surprised at the lack of endocardial electrogram abnormalities given the extent of LGE on CMR. We reviewed the maps and there was no lack of physical contact of the mapping catheter. The only explanation we can think of is overestimation of the...
extent of the LGE by the CMR. An epicardial approach should be performed first, owing to the frequent epicardial substrate.

Before ablation of VT, our patient experienced repetitive ICD therapies despite optimal medical treatment. Since ablation, our patient did not have any recurrence of VT, while the specific treatment was only started 6 months after the second procedure. We assume that efficacy of the treatment is related to both catheter ablation, which eliminated existing reentrant circuits, and specific treatment, which prevented the formation of new arrhythmogenic substrate. With this treatment, our patient has been freed from VT recurrence for over 36 months.

In the literature we identified only 7 cases of radiofrequency ablation of VT in patients with FD.11–15 This number seems small, considering the risk of arrhythmia in FD, and we assume that patients may have been ablated without being diagnosed. Hence, electrophysiologists performing ablation of a VT, especially when there is inferolateral epicardial substrate, should watch out for the previously mentioned signs of FD.

**Conclusion**

Late-onset FD is a rare cause of arrhythmia, but every cardiologist and electrophysiologist should be aware of red flags. Cardiac hypertrophy, even slight, and inferolateral wall abnormalities should raise a suspicion of FD. Extracardiac manifestations are often absent. A measurement of α-Gal A activity and genetic testing are the key to diagnosis. Epicardial substrate mapping and ablation could be a feasible option in case of recurrent arrhythmia despite pharmacological treatment.

**References**