Severe hypertrophic cardiomyopathy in a patient with atypical Anderson-Fabry disease

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Keywords: Anderson-Fabry disease • cardiac magnetic resonance • cardiomyopathies • echocardiography •enzymatic replacement therapy • sudden cardiac death

Abstract

Anderson-Fabry disease (AFD) is a hereditary disorder caused by a deficiency in the lysosomal enzyme α-galactosidase A which causes dysfunctions in multiple organ systems. Cardiac manifestation includes left ventricular hypertrophy, thickening of the valves, conduction disturbances and in the late phase, extensive areas of myocardial fibrosis with increased risk of sudden cardiac death. Case example: A case of AFD with exclusive cardiac involvement is described. During follow-up, due to the high risk of life-threatening arrhythmic events, implantation of an implantable cardioverter defibrillator is performed. Conclusion: AFD patients with advanced cardiac disease might represent a subgroup of patients who may require an implantable cardioverter defibrillator for primary prevention of sudden cardiac death.

Introduction

Anderson-Fabry disease (AFD) is a lysosomal storage disorder with an X-linked manner caused by a deficiency of α-gal A [1]. The decreased enzyme activity causes progressive, widespread intracellular accumulation of globotriaosylceramide and other sphingolipids throughout the body, leading to dysfunctions in multiple organ systems [2]. The incidence of AFD is estimated to be 1:40,000, however recent newborn screening has found a higher prevalence of the disease, from 1:3000 to 1:1500 male births [3,4]. In the classic form, AFD progresses slowly, with children and adolescents having neuropathic pain, angiokeratomas, dyshidrosis and gastrointestinal symptoms. Adults develop chronic kidney disease, cardiac involvement and premature stroke, which are important causes of death. Cardiac involvement, with left ventricular hypertrophy (LVH) and rhythm and conduction abnormalities is frequent in AFD and generally presents by the fourth decade of life. Atypical forms of AFD, predominantly affecting the heart, were reported almost a century after the original descriptions of the condition [5]. Sustained ventricular arrhythmias and sudden cardiac death have been observed in subjects affected by AFD [6]. A study of 1448 patients from the International Fabry Registry reported ventricular arrhythmias in 14% of affected men and 20% of women, which also manifested other signs and symptoms of AFD [7]. Here, we describe an atypical presentation of AFD with severe cardiomyopathy and ventricular arrhythmias, but with no other clinical manifestations referable to AFD. We briefly discuss management issues and the available evidence for primary prevention of sudden cardiac death with the implantable cardioverter defibrillator (ICD).

Case history

In April 2013, a 63-year-old male was admitted to our outpatient cardiomyopathy and heart failure unit for dyspnea and palpitations. The patient had a negative family history for cardiomyopathies, sudden death, no cardiovascular risk factor and comorbidities. A previous cardiac evaluation, including electrocardiography and echocardiography, performed approximately 10 years ago showed no pathological findings.

The ECG showed left anterior ventricular hemiblock and LVH with repolarization abnormalities in lateral leads (Figure 1). Routine laboratory tests (including proteinuria) were negative. Echocardiography showed severe concentric LVH with a maximal wall thickness of 27 mm, type I diastolic dysfunction, mild grade mitral regurgitation and left ventricular tract obstruction of 40 mmHg at rest (Figure 2), due to anterior displacement of papillary muscles and mitral subvalvular apparatus. 24-h ECG Holter monitoring showed a short run of non-sustained ventricular tachycardia of five beats and an average ventricular rate of 170 b/m (Figure 3). The patient also underwent a stress test, showing a five beat non-sustained ventricular tachycardia at peak exercise. Cardiac MRI with late postcontrast imaging was performed (Figure 4), confirming a severe, concentric left ventricular hypertrophy (index left ventricular mass = 209 g/m2) with diffuse late gadolinium enhancement, thickening and anterior apical displacement of papillary muscles.

Following our cardiomyopathy clinic protocol, as routinely performed in any male patient with hypertrophic cardiomyopathy (HCM) over 40 years of age (with or without proteinuria and other systemic sign raising suspicion of AFD), we performed enzymatic blood assay with dry blood spot. Dry blood spot revealed absence of α-gal A activity and genetic analysis showing a substitution of one cytosine with one guanine in position 901 of the cDNA GLA (Figure 5).

The patient started enzyme replacement therapy (ERT) with agalsidase-beta for 6 months and a second repeated cardiac MRI showed confirmed increased left ventricular mass index (from 255 to 270 g) and extensive myocardial fibrosis. After a discussion with nephrologists, neurologists, the electrophysiology team and cardiac transplant team surgeons, ERT was continued, with the hope of preventing mid-to-long term multiorgan damage and an ICD was implanted due to the high risk of life-threatening arrhythmic events.

Discussion

AFD is a clinically heterogeneous disorder which may result in a range of manifestations. AFD disease is not a rare disease but a disease underdiagnosed with a delay from the onset of symptoms to diagnosis of 15 years, which can contribute to the early death of such patients. A correct and early diagnosis of AFD is necessary to maximize α-gal

A replacement therapy effectiveness as the ERT efficacy is based on the ability to prevent further accumulation of glycosphingolipids in target cell lysosomes.

Cardiac involvement in AFD is well known. However, this usually occurs in the setting of multisystemic disease (especially renal involvement), or is associated with typical 'red flags' (short PR interval, atrioventricular block, increased atrioventricular valve thickness and increased right ventricle free wall thickness) [8]. In some cases, cardiac MRI could represent a fundamental step for the diagnosis of AFD in subjects with cardiomyopathies, mostly in the absence of other typical manifestations [9].

The localization of fibrosis in AFD cardiomyopathy has a few typical features [10]. It is characterized by the predominant involvement of the inferolateral basal (or mid-basal) segments and a mid-wall distribution sparing the subendocardium. However, diffuse fibrosis can be present in end-stage AFD cardiomyopathy, as in the present case.

ERT has recently been introduced as a therapy capable of enhancing α-Gal A plasma activity in AFD patients favoring the elimination and preventing further accumulation of globotriaosilceramide in tissues [11]. It is well known that the sooner the beginning of such therapy (i.e., before irreversible tissue damage occurs) the greater the benefits of the therapy itself. From a cardiovascular perspective, a recent study has shown that in patients without myocardial fibrosis, ERT results in a significant reduction in left ventricular mass, an improvement in myocardial deformation indices (i.e., global longitudinal strain) and a better performance at cardiopulmonary exercise testing (i.e., increase

in VO2 max) [12]. Conversely, in patients with myocardial fibrosis, ERT is unable to determine a reduction in ventricular mass and cardiopulmonary performance. Despite these limitations and some drawbacks (i.e., the need for intravenous administration every 2 weeks, the possibility of hypersensitivity reactions), ERT is currently the only effective therapy for AFD. Studies on chaperone therapy and gene therapy of AFD are also ongoing [13]. Complex ventricular arrhythmias and sudden cardiac deaths have been reported in AFD [14]. In a series of 78 patients with AFD, atrial fibrillation was seen in 17% of patients and non-sustained ventricular tachycardia in 8% [15]. However, presently there are no standard guidelines for ICD implantation in AFD cardiomyopathy, given the small number of patients, variable phenotypic expression of disease and scant data on risk factor for sudden cardiac death (Table 1). A potential strategy could be to use major prognostic features as applied in sarcomeric hypertrophic cardiomyopathy, such as severe hypertrophy, non-sustained ventricular tachycardia on Holter monitoring, unexplained syncope and abnormal blood pressure response on stress test and family history of sudden cardiac death, associated or not with minor features (i.e., myocardial fibrosis at MRI), in making decisions about ICD therapy. In our patient, according to the recent European Society of Cardiology guidelines for management of hypertrophic cardiomyopathy [16], we may consider an ICD based on a calculated sudden cardiac risk score of 5.8%. However, the anatomic background and the natural history of the two diseases, in other words, sarcomeric and AFD cardiomyopathy, are different and there is no data showing that the risk stratification is comparable. Interestingly, Weidemann et al. recently studied 40 patients with genetically proven AFD and treated prospectively with ERT for 6 years [17]. They showed that sudden cardiac death (n = 6; 15%) occurred only in patients with documented ventricular tachycardia and myocardial replacement fibrosis at MRI [17]. They conclude that, despite ERT, myocardial fibrosis and sudden cardiac death continue to develop in patients with advanced AFD cardiomyopathy [18]

Conclusion

Atypical forms of AFD with unusual, exclusive and significant cardiac involvement can be encountered in the clinical setting. According to our experience, AFD patients with advanced disease, in other words, severe hypertrophy LVH, ventricular arrhythmias and extensive myocardial fibrosis at MRI (which is not a common feature of the disease), might represent a subgroup of patients at major risk for life-threatening arrhythmias, who may require an ICD implantation for primary prevention of sudden cardiac death.

Future perspective

The challenges in the diagnosis and indications for treatment of AFD are part of today's clinical cardiology practice. Following the introduction of specific therapies (i.e., ERT) in the last decade, particular attention was paid to AFD, which has enabled the acquisition of important knowledge about its natural history, pathophysiology and response to therapy. A growing awareness of AFD within the cardiology community has increased the likelihood of patients to receive timely and correct diagnosis and therefore the appropriate therapy. Shortly, the growing experience of AFD treatment could clarify on the effect of ERT and chaperone therapy on the clinical course of the disease. It could also suggest the optimal age for the beginning of treatment and could help determine the need for neonatal screening.

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Figures and tables

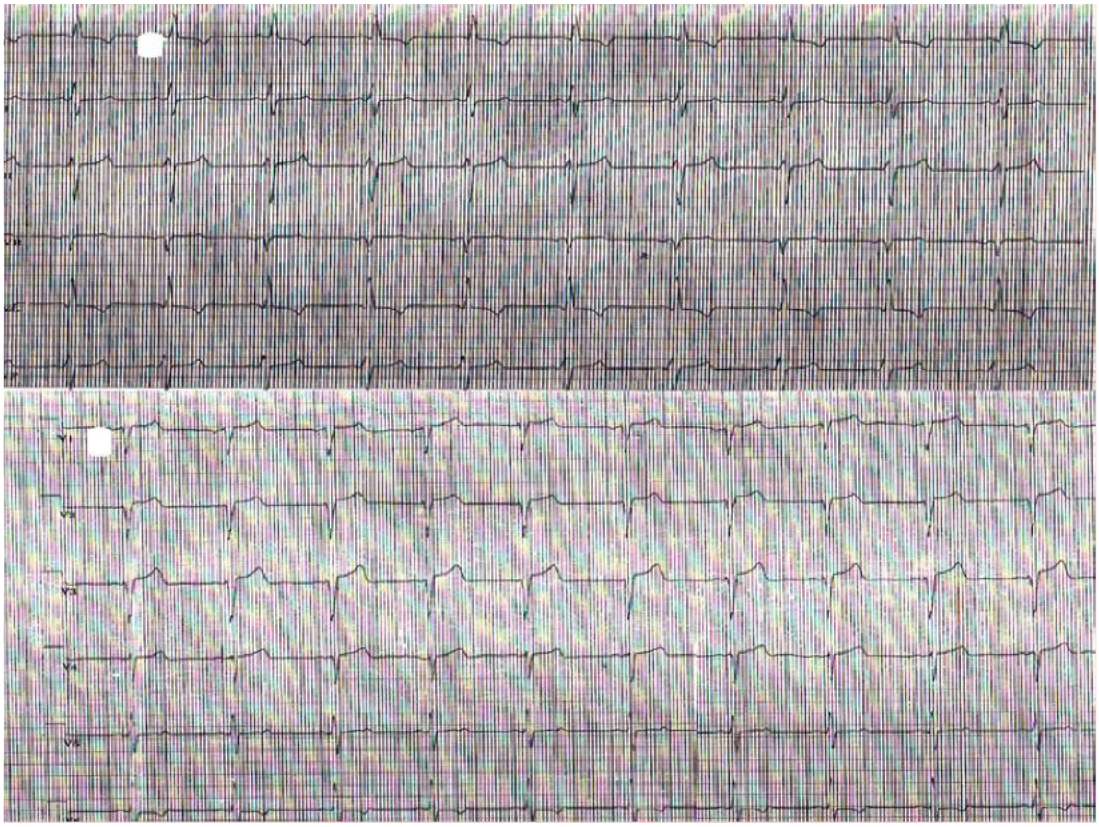

Figure 1. ECG shows left anterior hemiblock, left ventricular hypertrophy (R wave in AVL > 11 mm) with ventricular repolarization abnormalities in lateral leads.

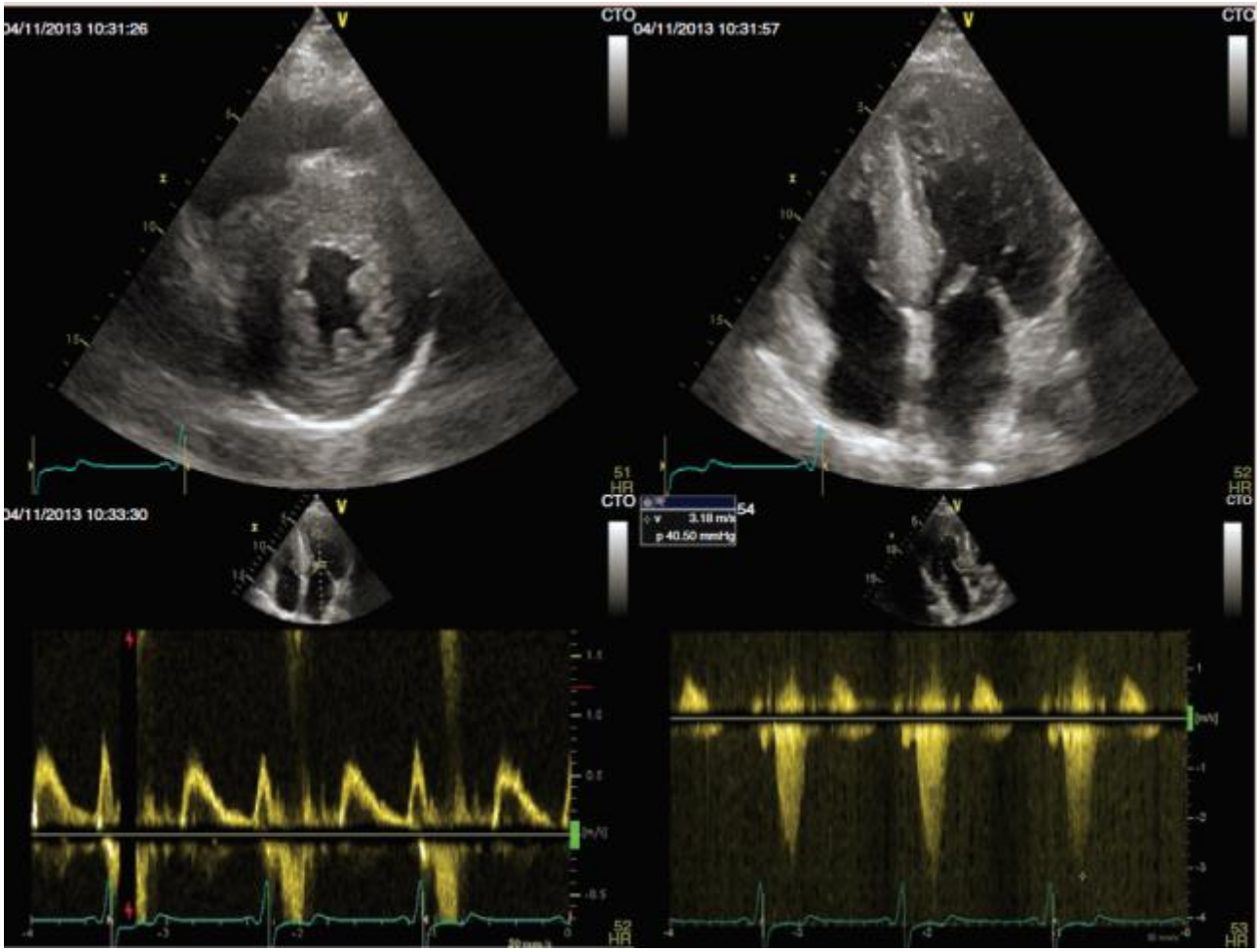

Figure 2. Echocardiography documented severe concentric and symmetric left ventricular hypertrophy with left ventricular tract obstruction of 40 mmHg at rest and abnormal ventricular relaxation.

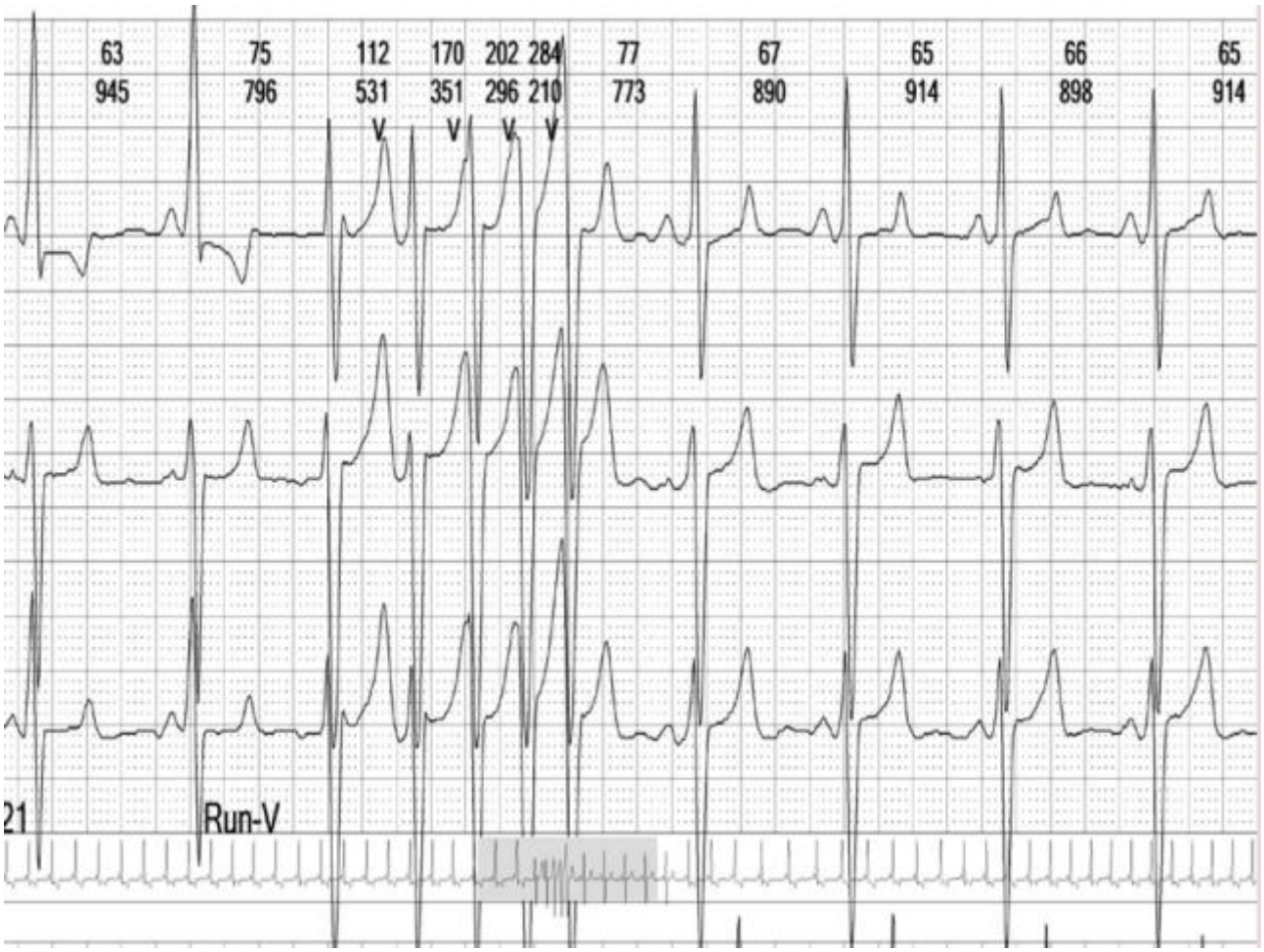

Figure 3. 24-h Holter monitoring showed a nonsustained ventricular tachycardia of five beats at medium ventricular rate of 170 b/m.

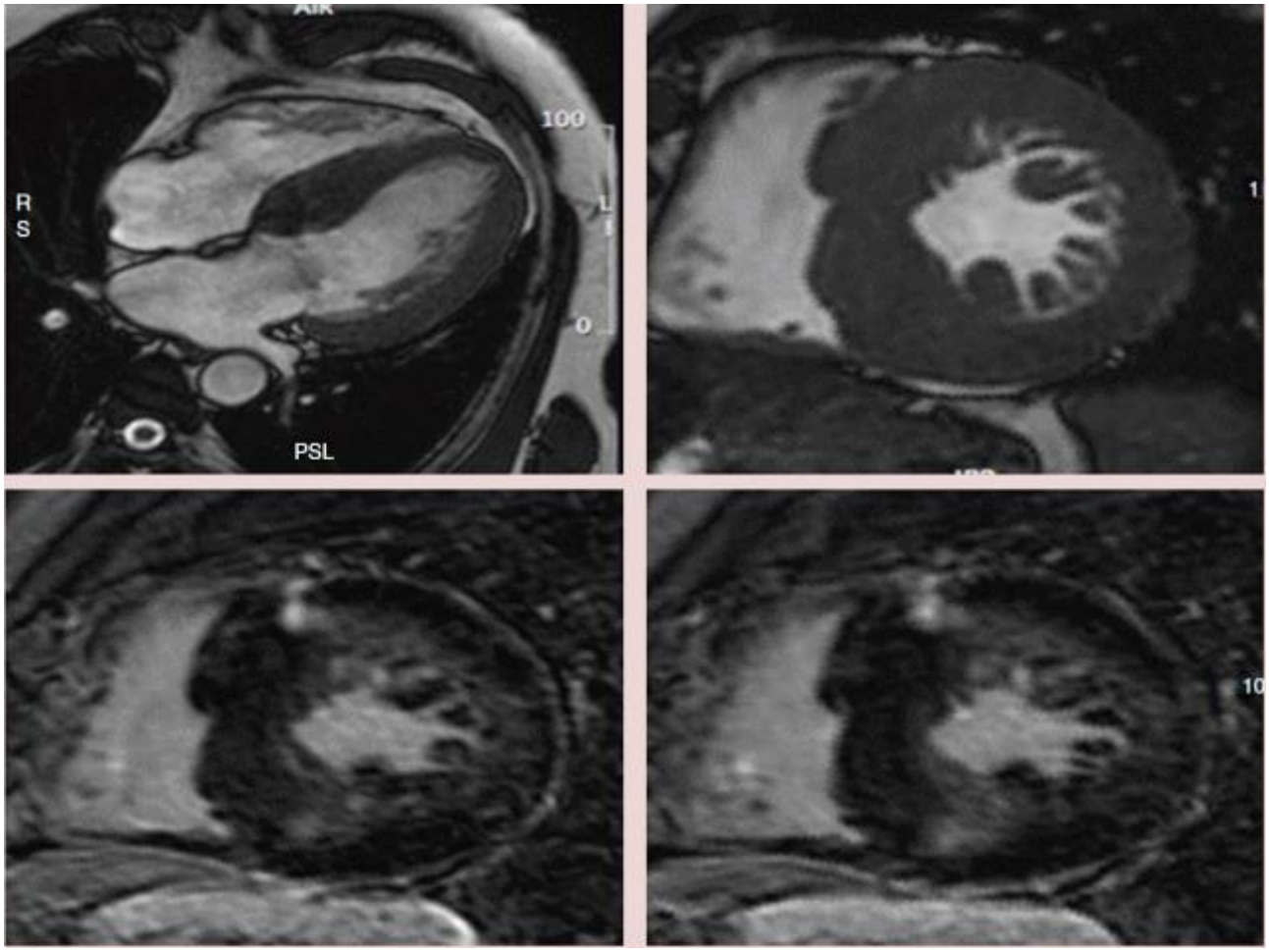

Figure 4. Cardiac magnetic resonance showing severe symmetric left ventricular hypertrophy with evidence of diffuse late gadolinium enhancement.

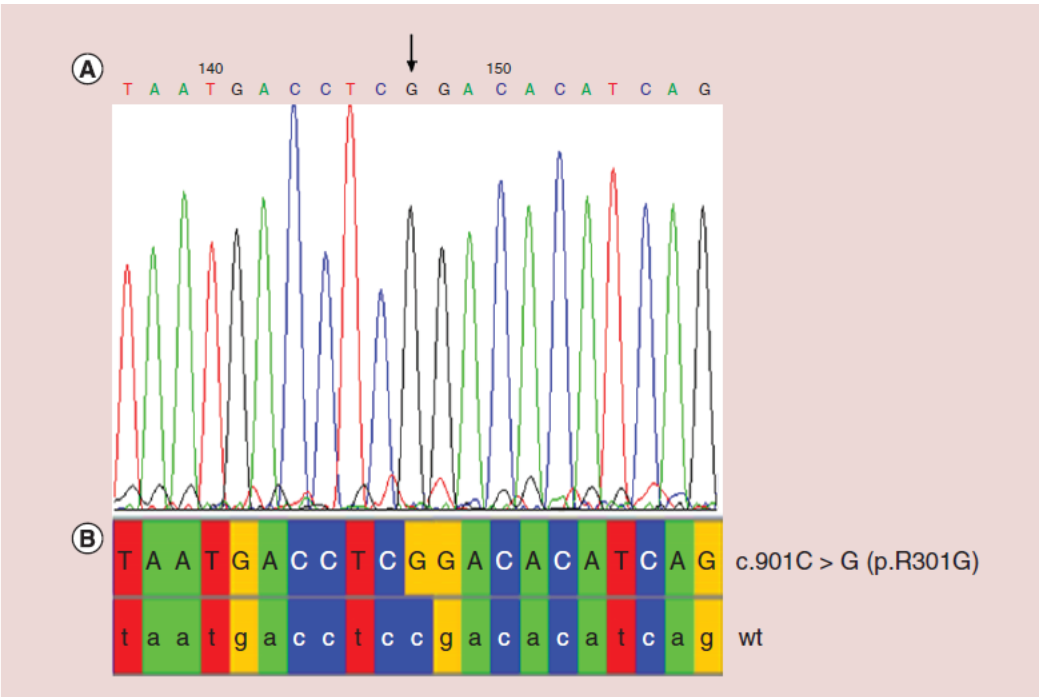

Figure 5. Mutation c.901C>G. (A) Portion of the electropherogram of exon 6 of the GLA gene of the patient, in which the mutation is indicated by the arrow. (B) Portion of the sequence of exon 6 of the GLA gene of the patient aligned with the corresponding sequence of the wild-type control.

Study (year)	Number of patients	PM/ICD implantation (%)	CV events, % (MI, HF, CV death)	SD (%)	Risk factor for SD/CV events
Linhart (2007)	714	3	NA	NA	LVMI
Patel (2011)	2869	NA	5	NA	LVMI, hypertension
Weidmann (2013)	40	NA	NA	15	Myocardial fibrosis
Talbot (2014)	25	NA	NA	15	LVMI, E/Ea ratio, glomerular filtration rate
Kramer (2014)	73	2	NA	6	Myocardial fibrosis
Patel (2015)	207	6	3	NA	Age, QRS duration, Mainz severity score index

CV: Cardiovascular; E/Ea ratio: Mitral Doppler inflow E wave velocity to annular tissue Doppler Ea wave velocity ratio; HF: Heart failure; ICD: Implantable cardioverter defibrillator; LVMI: Left ventricular mass index; MI: Myocardial infarction; NA: Not available; PM: Pacemaker; SD: Sudden death.

Table 1. Summary of the study on cardiovascular events in Anderson-Fabry disease.