Arrhythmias in Fabry Cardiomyopathy

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KEYWORDS

• Fabry disease • Cardiomyopathy • Bradycardia • Tachycardia • Arrhythmia • Pacemaker • Defibrillator

KEY POINTS

- Fabry cardiomyopathy is a multisystem disorder with important cardiovascular involvement.
- Arrhythmias can cause significant morbidity and mortality in Fabry disease.
- Fabry disease can be diagnosed by measurement of plasma α-galactosidase A or mutation analysis.
- Specific treatment consists of enzyme replacement with agalsidase alfa or agalsidase beta.
- Arrhythmias in Fabry disease can be treated with device or pharmacologic therapy.

INTRODUCTION

Anderson-Fabry disease (FD) is a multisystem disorder caused by the deficiency of α-galactosidase A, which leads to abnormal lysosomal accumulation of glycolipids. It is the second most common lysosomal storage disease, after Gaucher's disease. It is an X-linked disorder, but females can also be affected because of random X chromosome inactivation. Clinical findings include angiokeratomas, neuropathy, gastrointestinal symptoms, renal failure, stroke, and cardiovascular disease. Women typically have later onset, fewer symptoms, and slower progression than men. Life expectancy is decreased by 20 years in men and 10 to 15 years in women, and the principal cause of death is renal failure followed by cardiac and cerebrovascular causes.[1,2] Treatment involves enzyme replacement therapy (ERT) with agalsidase alfa or agalsidase beta. Early treatment leads to improved clinical outcomes.

CARDIOVASCULAR MANIFESTATIONS

Left ventricular hypertrophy is the most common cardiac manifestation (**Figs. 1–3**).[3] The hypertrophy can be related to abnormal lysosomal storage and myocyte hypertrophy and fibrosis.[4] The hypertrophy can be so severe that it resembles hypertrophic cardiomyopathy. In fact, 1% to 6% of patients presenting with hypertrophic cardiomyopathy may have FD by genetic analysis.[5,6] Coronary and cerebrovascular disease and microvascular dysfunction may be present. Valvular regurgitation is frequently observed by echocardiogram but typically not clinically significant.[5] Patients can present with angina, myocardial infarction, palpitations, syncope, and heart failure.[6] Hypertrophy is usually the primary cardiac presentation in women. However, women in particular can have fibrosis without hypertrophy.[7] Arrhythmias are important causes of morbidity and mortality in FD and are the focus of this article.

ELECTROCARDIOGRAPHIC FINDINGS

The first electrocardiographic descriptions in FD were those of abbreviated PR intervals.[8,9] Subsequent series described short PR intervals and atrioventricular (AV) block, sinus node dysfunction,

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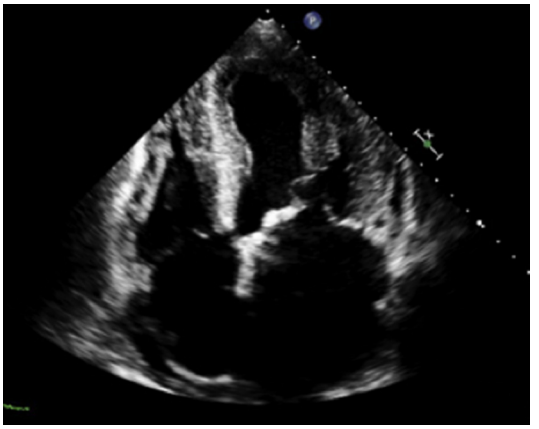

Fig. 1. Apical 4-chamber view of a patient with FD shows hypertrophied right and left ventricles and biatrial enlargement.

intraventricular conduction delay, right bundle branch block, atrial enlargement, left ventricular (LV) hypertrophy, and ST-T changes (**Fig. 4**).[10–13] Short PR intervals and ST-T changes can be restored to normal with enzyme replacement therapy.[14,15] In a study of 207 patients with FD, PR interval shortening was found in 14% and AV block in 1.4%.[16] In another study of 30 patients with FD compared with controls, P wave duration, PR interval, and QRS width are shorter in patients with FD.[17] In a cross-sectional study of 150 patients with FD, there was a positive correlation between LV mass on cardiovascular magnetic resonance and QRS duration and the Sokolow index for left ventricular hypertrophy (LVH) on electrocardiogram, and the absence of ST or T alterations on electrocardiogram excluded late enhancement on cardiovascular magnetic resonance.[18]

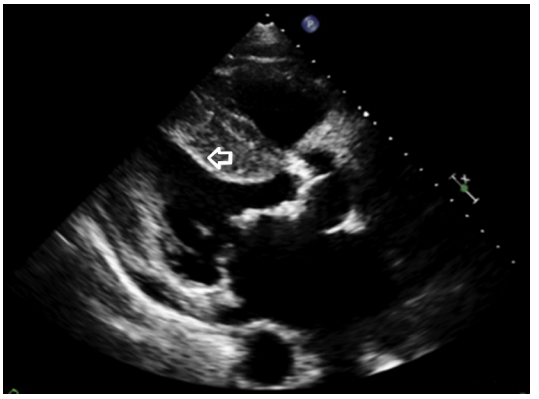

Fig. 2. Left ventricular hypertrophy with a characteristic endocardial stripe (*arrow*) and thinning of the basal posterolateral wall in an FD patient.

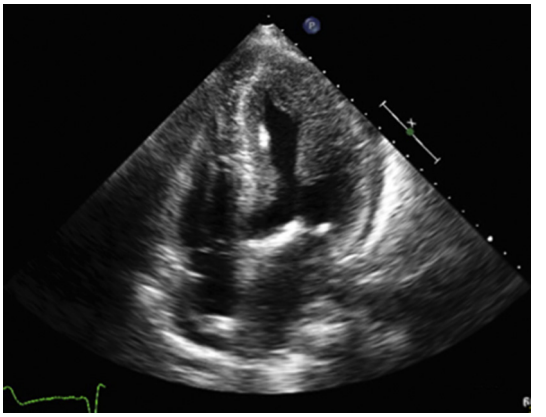

Fig. 3. Severe hypertrophy and narrowing of the LV outflow tract in a man with FD.

BRADYCARDIA

Patients with FD can have sinus node dysfunction, AV nodal disease, or His-Purkinje system disease. Sinus bradycardia may be poorly responsive to atropine.[19] AV conduction abnormalities can occur without other cardiovascular manifestations and may be related to infiltration of the conduction system.[19,20] A longitudinal study of 204 patients with FD showed that QRS duration and PR interval duration increased with age and were independent future predictors of need for pacemaker.[21] Patients who have pacemakers and defibrillators have high utilization of pacing in atria and ventricles.[22]

TACHYCARDIA

A longitudinal study of arrhythmias in FD followed up with 78 patients for 1.9 years. There was 1 sudden death, 4 patients received pacemakers, and 1 patient received a biventricular implantable cardioverter defibrillator (ICD). Of the 60 patients in this cohort who underwent Holter monitoring, 3.9% had persistent atrial fibrillation, 13.3% had paroxysmal atrial fibrillation, and 8.3% had nonsustained ventricular tachycardia. Age was an independent predictor of atrial fibrillation.[23] A review of the 1448 untreated patients with FD showed a 13% incidence of ventricular arrhythmias in men and 20% in women, highlighting the significant arrhythmic risk in women.[24] Clinically significant ventricular tachycardia, ventricular fibrillation, atrial tachycardia, atrial flutter, and supraventricular tachycardia have all been described in individual cases and series.[25–28] In a long-term study of 40 patients, 6 patients had sudden cardiac death (SCD), and these patients all had previously documented ventricular tachycardia and

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