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Case Report

Early onset development of hypertrophic cardiomyopathy in less than 1 year in a patient with familial Friedrich's ataxia: Case report ☆

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ABSTRACT

Friedreich's ataxia (FRDA) is a neurodegenerative disease characterized by progressive ataxia, dysarthria, sensory loss. While neurological symptoms are prominent, cardiac manifestations significantly contribute to mortality. Cardiomyopathy in Friedreich's disease results from mitochondrial dysfunction, loss of contractile proteins and an accumulation of fibrosis in heart. To better characterize the severity of cardiac involvement, the MICONOS study group developed a classification system categorizing FRDA cardiomyopathy as "no," "mild," "intermediate," "severe."

We report an uncommon case of early-onset development of hypertrophic cardiomyopathy (HCM) in a 25-year-old female diagnosed with Friedreich's ataxia (FRDA) at age 12. Through annual cardiac evaluations, no signs of cardiac disease were noted. Until presenting with dyspnea and palpitations. Clinical examination revealed truncal ataxia and dysarthria, but no signs of heart failure. However, a transthoracic echocardiography demonstrated nonobstructive hypertrophic cardiomyopathy with a maximal wall thickness of 20 mm, incomplete anterior systolic motion of the mitral valve, a significant development in less than 1 year after last normal cardiac assessment. Left ventricular systolic function was preserved (ejection fraction 50%). She was prescribed bisoprolol and dapagliflozin, with significant improvement at her latest checkup. Family screening revealed HCM in her 30 year female sibling, who also has FRDA. No cardiac abnormalities were detected in her younger brother or parents.

Friedreich's hypertrophic cardiomyopathy has been reported as the most significant cause of mortality, especially among younger patients with early onset disease manifestations.

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Introduction

Friedreich's ataxia (FRDA) is a neurodegenerative disease with autosomal recessive inheritance pattern, caused by a lack of a protein called frataxin (FXN), which is essential for mitochondrial function [1]. Patients with FRDA experience progressive ataxia, dysarthria, sensory loss, and pyramidal signs [2].

While the progressive, irreversible ataxia and neuromuscular deterioration associated with FRDA are widely acknowledged, significant mortality arises from cardiomyopathy [1]. Cardiac manifestations are prevalent among FRDA patients and is considered a considerable factor to premature mortality. Historically categorized as a hypertrophic cardiomyopathy, the cardiac phenotype of FRDA is increasingly recognized for its heterogeneity. For instance, prior investigations have indicated that the hypertrophic heart in FRDA patients may undergo a transition to a dilated state [2], and the MICONOS study group had proposed a severity classification of FDRA's cardiomyopathy into "no", "mild", "intermediate" and "severe" [3].

In this article, we report an uncommon case of familial hypertrophic cardiomyopathy development in a female patient-diagnosed with Friedrich's Ataxia.

Case presentation

This case involves a 25 year old female patient with a medical history of Friedrich's ataxia, the first manifestations of the disease begun early at the age of 12 years old, progressively the patient presented symptoms of cerebellar ataxia, dysarthria, and muscle weakness of lower limb. Ten years after diagnosis, the patient became wheelchaired. Her family history was also known for familial neurodegenerative disease: a 30 year old female sibling with a Friedrich ataxia, and a younger brother with no evidence of disease penetrance, with no family history of sudden cardiac death.

The patient begun her follow up in cardiology department 6 years after diagnosis, since she presented with symptoms of palpitations and atypical chest pain, the annual cardiac checkup included a 12-lead-electrocardiogram that revealed negative T waves in lateral leads, an annual trans thoracic-echocardiography was performed every year for 7 years, and showed no evidence of cardiomyopathy. The patient was prescribed bisoprolol 5 mg per day.

Until this year's cardiac checkup, when the patient presented to our department with symptoms of palpitations and New York Heart Association (NYHA) class II dyspnea, which she had been experiencing for the last 5 months. She also reported having a general tiredness, and anorexia. However, there was no history of lipothymia or syncope, or other functional signs.

Upon general examination, the patient appeared eupneic at rest with a heart rate of 75 beats per minute, a blood pressure of 122/67 mmHg, a temperature of 36.8°C, room air oxygen saturation was consistently 98%. Cardiovascular examination revealed no abnormal sounds of heart, no signs of heart failure, and no gallops, murmurs or rubs were noticed. Pulmonary auscultation revealed clear breath sounds with no evidence of wheezes, rhonchi, or crackles. Neurological examination had revealed a truncal ataxia, paraparesis of both lower limbs, absent deep tendon reflexes, and dysarthria, while the motor function of both upper limbs is preserved. The rest of general examination was normal.

The 12-lead electrocardiogram (EKG) (Fig. 1) revealed regular sinus rhythm at 64 beats per minute, electrical left ventricular hypertrophy (following Cornell index), and presence of negative T waves in lateral and apical leads (Fig. 1). On the 24-hour Holter EKG no ventricular or supraventricular arrhythmias were registered.

The transthoracic echocardiography was evident for hypertrophic cardiomyopathy with left ventricular (LV) hypertrophy: a maximal wall thickness of 20 mm and a septal wall thickness of 17 mm, a hypertrophic right ventricular wall at 9 mm, and an enlarged inter-atrial septum at 8 mm, with an incomplete anterior systolic movement of the mitral valve, and a left atrial diameter of 31 mm (Fig. 2).

No left ventricular outflow tract (LVOT) obstruction was noted at rest or during exercise (Maximal gradient at 3.35 mmHg at rest and 5 mmHg after Valsalva maneuver), and a maximal gradient post ventricular extrasystole at 10.69 mmHg (Fig. 1). The systolic function of the left ventricle was preserved at 50%. Nevertheless, an alteration of at −11% was noted at the global longitudinal left ventricular strain performed, with regional alteration in anterior and latero-posterior segments as shown in Fig. 3.

The study of left ventricular diastolic function revealed a type II mitral profile, with a peak E velocity at 0.7 m/s, an E/E' ratio at 6.59. A valid criterion for the evaluation of LV diastolic function in HCM is the pulmonary A-wave (Ap)duration, which was 209 ms in this case superior to the mitral A wave (Am) duration of 114 ms, with Ap-Am >30 ms.

Laboratory tests showed normal blood cell counts, and a C-reactive protein at 0.5 g/dL, which is a marker of inflammation. Troponin levels, which indicate heart muscle damage, were normal at 5 ng/L (normal inferior to 10 ng/L), the proBNP test showed a high level, reaching a 3500 mg/L. Kidney and liver function were also normal, and Hb1ac was at 37 mmol/mol excluding diabetes in this case, since its occurrence in Friedrich's ataxia is well described. The rest of biological findings were also normal.

The risk of sudden cardiac death at 5 years was low at 1.96%, calculated with HCM-risk SCD score, indicating no need to implantable cardioverter-defibrillator (ICD) in this case. Thus, therapeutically the patient was prescribed a daily treatment including betablockers: bisoprolol 10 mg per day to improve palpitations, and SGLT2 inhibitors: dapagliflozin 10 mg/day to help improve her ejection fraction and dyspnea symptoms.

During the last check-up, the patient had significant improvement in symptoms, she was no longer dyspneic, and had less paroxysmal episodes of palpitations. ProBNP level had dropped to 290 ng/L, showing a significant improvement.

Family screening carried out including EKG and transthoracic echocardiography showed clear signs of hypertrophic cardiomyopathy in the older female sibling: with LV septal and posterior wall thickness of 19 mm and 13 mm respectively,

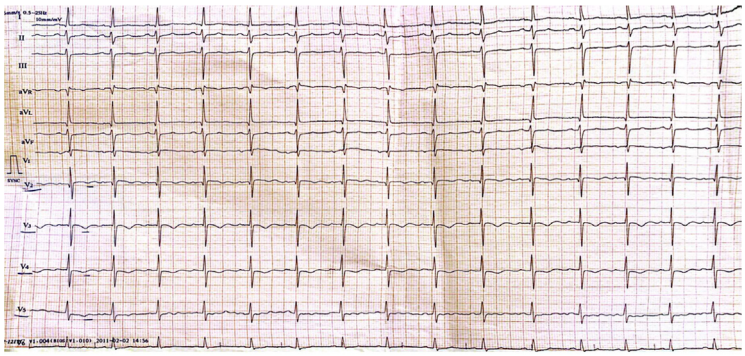

Fig. 1 – Electrocardiogram showing electrical LV hypertrophy and negative T waves.

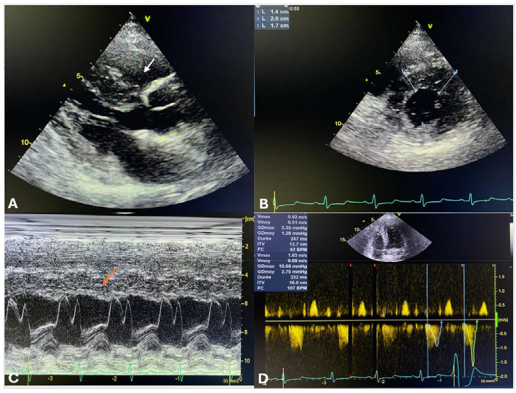

Fig. 2 – Transthoracic echocardiography revealing a hypertrophic cardiopathy. (A) septal wall thickness at 17 mm "white arrow", (B) demonstrating maximal and septal wall thickness. (C) Systolic anterior movement of mitral valve (orange arrow). (D) Maximal gradient at rest and after ventricular extrasystole.

maximal gradient at 16.37 mmHg at rest and effort, the systolic left ventricular function was normal at 60%, she experienced no signs of heart failure: no dyspnea, no chest pain and no palpitations (Fig. 4). On the other hand, no cardiac manifestations were noted among the healthy brother, nor in the parents.

Discussion

Friedreich's ataxia (FRDA) is the most common inherited neuromuscular degenerative disease, transmitted in an autosomal recessive pattern, with an incidence of 1 in 50,000 live births, and an equal frequency between sexes [4]. FRDA is most clinically recognized for its ongoing and worsening ataxia and neuromuscular degeneration, but substantial mortality is caused by cardiomyopathy. Variable phenotypes were described, and individuals can be categorized into early-onset or late-onset groups based on symptom onset before or after the age of 25, respectively [5]. Late-onset FRDA tends to have less severe cardiomyopathy and neurological symptoms, while early-onset typically shows faster progression with higher morbidity and mortality, with most patients becoming wheelchair-bound between 19 and 26 years, and dying on average by 39 years old [1].

On a genetic level, the condition is mainly due to a GAA triplet repeat expansion in the first intron of the frataxin gene (FXN) located on chromosome 9q21.11 [3]. This decreases the transcription and expression of frataxin, a protein in the mitochondrial inner membrane, potentially restricting ATP production in patient skeletal muscle and heart [3]. Moreover, the extent of energy deficiency in these patients showed a strong correlation with the degree of cardiac hypertrophy [6].

The clinical manifestations in Friedreich ataxia includes the neurological syndrome well-defined by the ICARS score

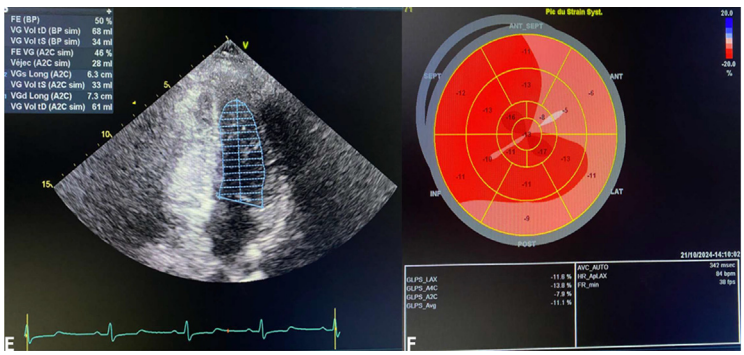

Fig. 3 – Transthoracic echocardiography demonstrating preserved ejection fraction (E) and altered global strain (F).

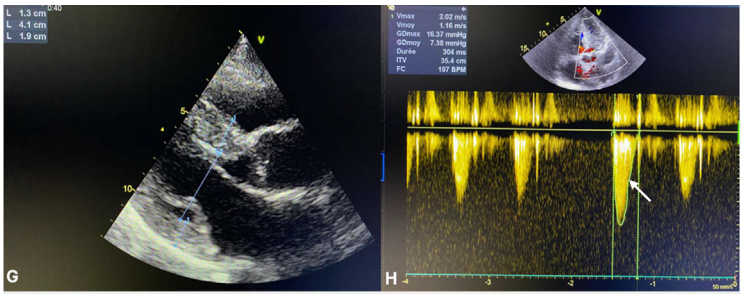

Fig. 4 – Transthoracic echocardiography of the female sibling with FRDA revealing a hypertrophic cardiomyopathy, and a maximal gradient at rest 16.37 mmHg (white arrow).

(International Consensus Ataxia Rating Scale), evaluating oculomotor function, speech, kinetic functions, posture, and gait. It is widely used in clinical practice, provides prognostic insights, and helps stage the patient's neurological involvement [7].

In contrast, Friedreich cardiomyopathy (CM) is less clearly defined. Recently, a basic algorithm for staging cardiac involvement was proposed, primarily based on echocardiographic morphology and global left ventricular (LV) function. However, it is well-established in other forms of hypertrophic CM that electrical abnormalities, myocardial fibrosis, and biomarkers of cardiac involvement are also crucial for a comprehensive assessment to describe the stage of cardiac involvement [7].

Cardiomyopathy in Friedreich's disease (FM) results from mitochondrial dysfunction, loss of contractile proteins and an accumulation of fibrosis in the heart. The left ventricle thickens, and may progress to hypertrophy or dilatation [8]. Dilated cardiomyopathy, often associated with arrhythmias, is the main cause of mortality [13]. The severity of cardiomyopathy is related to the age of onset of neurological symptoms and the length of genetic expansion (GAA repeat), but not necessarily to the duration of the disease or the severity of neurological symptoms [8]. In this context, cardiac MRI can help detect early abnormalities, such as fibrosis and alterations in cardiac structure, even before the onset of obvious symptoms of heart failure [9,12]

The MICONOS study group proposes classifying FA-CM into 4 categories: "no," "mild," "intermediate," and "severe" [3], using the following parameters: an ejection fraction (EF) of less than 55% for global left ventricular (LV) function, left ventricular posterior wall thickness (LVPWT) of 11 mm or more for hypertrophy, late enhancement (LE) of the myocardium for myocardial replacement fibrosis, high-sensitivity troponin T (hsTNT) levels of 14 ng/mL or more for myocyte damage, and T-wave inversion for repolarization abnormalities. If all these parameters were normal in a patient, the heart was classified as having no CM. An EF less than 55% was used to define end-stage CM, and presence of myocardial fibrosis defined severe CM. For cases between these extremes, the presence of LV hypertrophy (LVPWT $\geq$ 11 mm) was used to distinguish mild CM (no hypertrophy) from intermediate CM [3].

Following the MICONOS criteria, our patient would have developed a severe form of hypertrophic cardiomyopathy (LV wall thickness of 20 mm, and an EF of 50%), and this has been widely described in several studies, that early onset manifestations of FDRA's disease is characterized by a severe progression of the disease and development of cardiovascular manifestations at a younger age.

Beyond cardiomyopathy, other cardiac manifestations in FA are likely due to myocardial fibrosis and scarring. These changes predispose individuals to atrioventricular conduction blocks and both tachy- and brady arrhythmias, although atrial arrhythmias are relatively uncommon, and ventricular arrhythmias are even rarer [6].

Routine screening of cardiomyopathy may be more beneficial than relying solely on symptom review in FRDA patients, making the use of current imaging techniques advisable. A 2014 consensus statement on the multidisciplinary treatment of FRDA patients recommended performing an EKG and echocardiography at the initial evaluation and referring patients to a cardiologist only if cardiac symptoms or abnormal cardiac test results are present. However, we believe that patients should undergo annual screening with both an EKG and a transthoracic echocardiography [1]. Additionally, cardiac MRI, detecting remodeling and reduced myocardial perfusion reserve, may prove valuable in the future for early disease detection and monitoring therapeutic responses [6].

In terms of therapeutic strategies, a study by Buyse G et al. [10] which included 8 patients, a significant reduction in cardiac hypertrophy was observed in 6 out of 8 patients after 1 year of Idebenone therapy. This reduction in hypertrophy was preceded by early improvements in cardiac function [10,11].

While disease-specific therapies for Friedreich's ataxia (FA) are still under development, current management focuses on addressing the cardiac complications as they arise. Therefore, patients with FA experiencing heart failure symptoms, reduced left ventricular function, or arrhythmias are treated using standard heart failure medications, antiarrhythmic drugs, and, when appropriate, device implantation [3,14].

Conclusion

This case highlights the importance of cardiac evaluation in all patients with Friedreich's ataxia (FA), even those without cardiac symptoms. Early detection of cardiac involvement is crucial, as hypertrophic cardiomyopathy is a leading cause of death, particularly in younger patients with early-onset FA.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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