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FRIEDREICH'S ATAXIA AND ITS CARDIOVASCULAR MANIFESTATIONS

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SUMMARY

Friedreich's Ataxia is a disease characterized by modification of the FRDA gene on chromosome 9q13. Affection of this protein induces altered expression of frataxin. When this is altered, molecular changes and cell death arise due to iron accumulation in the mitochondria and elevation of reactive oxygen species.

The damage occurs mostly in neurons, causing neuronal impairment; however, alterations also occur in the heart, causing cardiac fibrosis. Symptomatology presents in adolescence, with peripheral sensory neuropathies, vestibular changes, hyporeflexia, myoclonias and dysarthria. Systemic manifestations include cardiomyopathies, diabetes mellitus and foot deformity. Specifically in the heart, the myocardium becomes hypertrophic with thickening of the ventricular walls, which subsequently progresses to heart failure and death.

The aim of this bibliographic review is to inform the scientific community of the presence of systemic manifestations, especially cardiovascular, in Friedreich's Ataxia; since this disease is not only characterized by the presence of neurological alterations, but also of affections to different apparatuses and systems of the human body, such as the heart, due to the cellular alteration that Friedreich's Ataxia causes.

KEY WORDS: ***Cardiomyopathy, Friedreich's ataxia, heart failure, frataxin, mitochondria, mitochondria***

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INTRODUCTION

Friedreich's ataxia is an autosomal recessive neurodegenerative disease, most prevalent in adolescents and young adults. A large number of patients usually present with left ventricular hypertrophy. It should be noted that the life expectancy of these patients is significantly low, reaching 40 years, and 60% of patients die of cardiac causes (1). This disease causes loss of motor skills and the inability to walk within 10 to 15 years from the onset of the disease due to neuro-degeneration of the dorsal ganglion root, the manifestations of which are based on debilitating scoliosis and the onset of severe hypertrophic cardiomyopathy (2).

Aetiology

This pathology is mostly caused by expansion of the GAA gene triplet and loss of function in the frataxin gene on chromosome 9q21.11 (3). There is a correlation between the GAA triple repeat and the onset and severity of symptoms; while a normal gene would have between 7 and 34 repeats, there can be as many as 66-1700 trinucleotide repeats, being associated with more severe disease and the presence of cardiomyopathy. Larger GAA expansions are associated with earlier disease onset, faster progression of muscle weakness, higher frequency of cardiomyopathy and upper limb areflexia.

Repetitions between 34 and 100 rarely cause disease. However, uninterrupted repeats are considered pre-mutations and can expand to more than 300 repeats in a single generation. In relation to frataxin, iron accumulates within mitochondria, reacting with oxygen to generate free radicals and at the same time reducing mitochondrial antioxidant capacities. Frataxin deficiency ultimately results in cell death, particularly of neurons, cardiomyocytes and pancreatic beta cells. These repeats lead to reduced transcription of the frataxin gene, which silences it and reduces frataxin production. Studies have shown a link between frataxin deficiency and the inactivation of iron and sulfur clusters in mitochondria. Thus, the mechanism of mitochondrial iron homeostasis is altered by the decrease in fraxatin, which translates into decreased energy levels and the subsequent degree of cardiac hypertrophy that this can cause. However, this is not the only cause. Iron deposition in cardiomyocytes has been shown to contribute to hypertrophy, suggesting oxidative tissue damage mediated by iron toxicity (4)(5).

Prevalence

Friedreich's Ataxia is the most common ataxia, accounting for 50% of all cases of ataxia and 75% of patients under 25 years of age. It is most common in patients of Western European descent. Worldwide, the prevalence is 1 per 40,000 people. The carrier rate of this type of ataxia is 1 in 75. As an autosomal recessive disease, it affects males and females equally. The age of onset is usually in adolescence, most commonly between 8 and 15 years of age (5).

Pathophysiology

The hallmark of Friedreich's Ataxia is reflected in the abnormality in the central sensory pathways, which are found in the posterior column of the spinal cord, the spinocerebellar tracts, the cerebellar efferent pathways and the distal portion of the corticospinal motor tracts. Other abnormalities include atrophy of cerebellar regions, such as the dentate nucleus.

Peripheral nerves show a loss of long myelinated sensory fibers, resulting in the loss of primary sensory neurons in the dorsal ganglion root of the spinal cord; the result of which may progress to cerebellar-like alterations and sensory ataxias, which characterize this disease. Cardiac involvement is caused by a mitochondrial disorder (mentioned above), resulting in mitochondrial proliferation, loss of contractile proteins and subsequent development of myocardial fibrosis. In addition, left ventricular involvement is such that the left ventricle becomes thickened and manifests as hypertrophy (symmetrical or asymmetrical) or dilated cardiomyopathy (6) (7) (8).

Cardiovascular clinical manifestations

Heart disease occurs in 2/3 of all patients with Friedreich's Ataxia and is a frequent cause of death, especially hypertrophic cardiomyopathy (9)(10). Rarely before neurological manifestations, and even if the patient is referred to a cardiologist, the neurological manifestations will be evident first; however, these manifestations precede the cardiac manifestations. However, the absence of cardiovascular symptoms in the presence of neurological manifestations leads us to suspect mosaicism of the GAA triplet expansion and somatic instability of the tissue. Cardiovascular symptomatology manifests with hypertrophic cardiomyopathy or left ventricular hypertrophy in 28-100%.

Cardiac angina and cardiac ischaemia are uncommon. Asymmetric septal hypertrophy or dilated cardiomyopathy are less common, and rather, are a progression of hypertrophic cardiomyopathy (11). Fifty-six percent of patients with Friedreich's Ataxia are characterized by heart failure within 6 months. The cardiomyopathy present in these patients is characterized by left ventricular hypertrophy and a normal or near-normal ejection fraction, associated with symptoms of heart failure caused by left ventricular diastolic dysfunction, either by impaired relaxation or increased left ventricular stiffness. Progression of left ventricular dilatation coupled with systolic dysfunction is associated with a worse prognosis (12)(13).

Diagnosis

Diagnosis is based on the detection of pathogenic variants of FXN.

- Normal alleles: 5-33 GAA repeats. More than 80-85% of alleles contain less than 12 repeats and approximately 15% have 12-33 repeats. Normal alleles greater than 27 GAA repeats are very rare.
- Normal mutated alleles: 34 - 65 GAA repeats. Although the exact frequency of these alleles has not been formally determined, the frequency of occurrence is less than 1%.
- High penetrance alleles: 66 to 1300 GAA repeats. Most expanded alleles contain between 600 - 1200 GAA repeats.
- Borderline: 44 - 66 GAA repeats. The length of the

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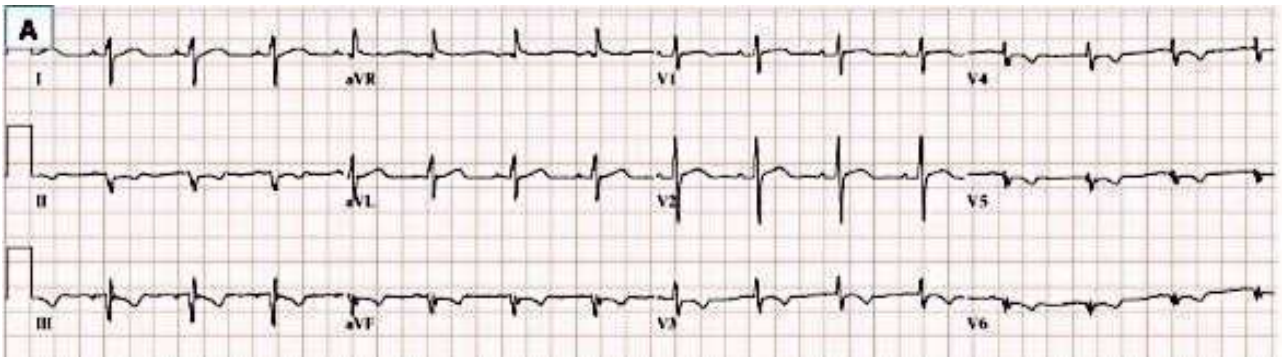
repeat has not been clearly determined whether or not the disease is present (14).

Cardiovascular Diagnosis

Electrocardiography: Electrocardiography is abnormal in almost all cases. The rhythm is usually sinus rhythm, including tachycardia, although the patient may present with supraventricular arrhythmias, particularly atrial fibrillation, atrial flutter, or atrioventricular reentrant tachycardia. The most common finding is T-wave inversion at the infero-lateral or generalized level. Other findings include ST-segment abnormalities, such as ST-segment elevation or depression, as well as T-wave abnormalities with T-wave flattening. When left ventricular hypertrophy is found on the electrocardiogram, the echocardiogram will always show hypertrophy. Axial deviation is very often found deviated to the right (15)(16).

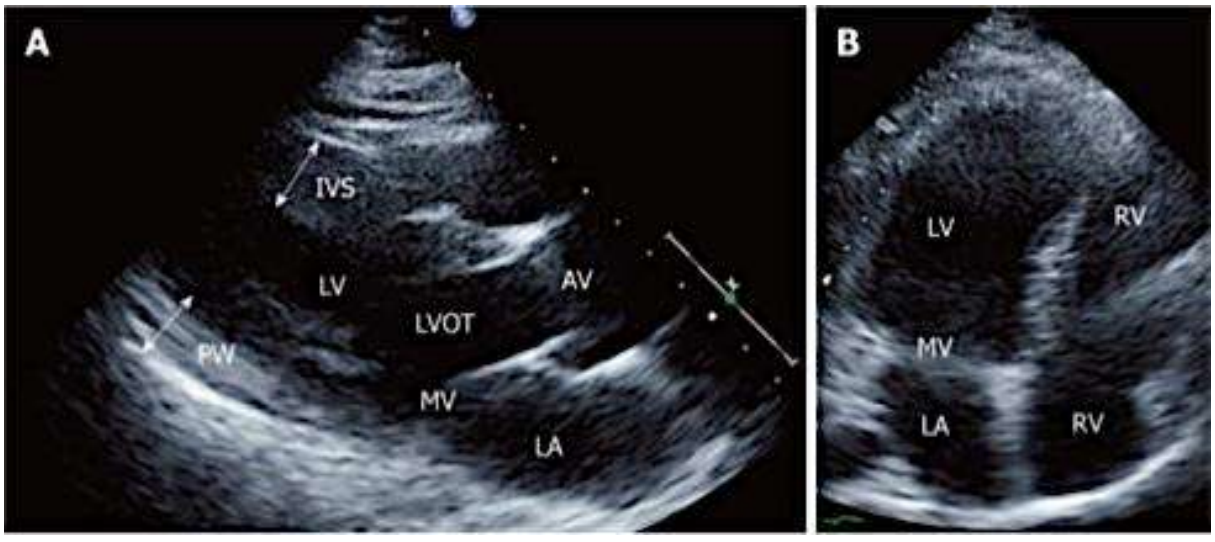
Illustration 1. Electrocardiogram with inferolateral Q-waves



Source: Cardiomyopathy in Friedreich's Ataxia. Salazar P, Indorkar R, Dietrich M, Farzaneh-Far A. Eur Heart J. 2018;39(7):631

***Echocardiography*:** This study most frequently demonstrates concentric left ventricular hypertrophy, but may also show asymmetric septal hypertrophy in other cases. Altered systolic function with relative preservation of ejection fraction may also be evident. However, the ejection fraction decreases with increasing age. In addition, papillary muscle hypertrophy is demonstrated (16).

Two-dimensional echocardiogram in a patient with Friedreich's Ataxia, with evidence of thickening of the posterior wall and interventricular septum in Figure A. Figure B shows dilatation of the left ventricular cavity.



Source: Heart disease in Friedreich's ataxia. Hanson E, Sheldon M, Pacheco B, Alkubeysi M, Raizada V. World J Cardiol. 2019;11(1):1-12.

***Cardiac MRI*:** The study relates the number of GAA triplet repeats to the degree of cardiac remodeling, and even to the age of onset of the pathology. The mass of the left ventricle decreases with the amount of time since the onset of the disease (more than 15 years), which leads to the presumption of cardiac thinning as the disease progresses. Adenosine can also be used in this study to determine the degree of myocardial perfusion, which in these patients with Friedreich's

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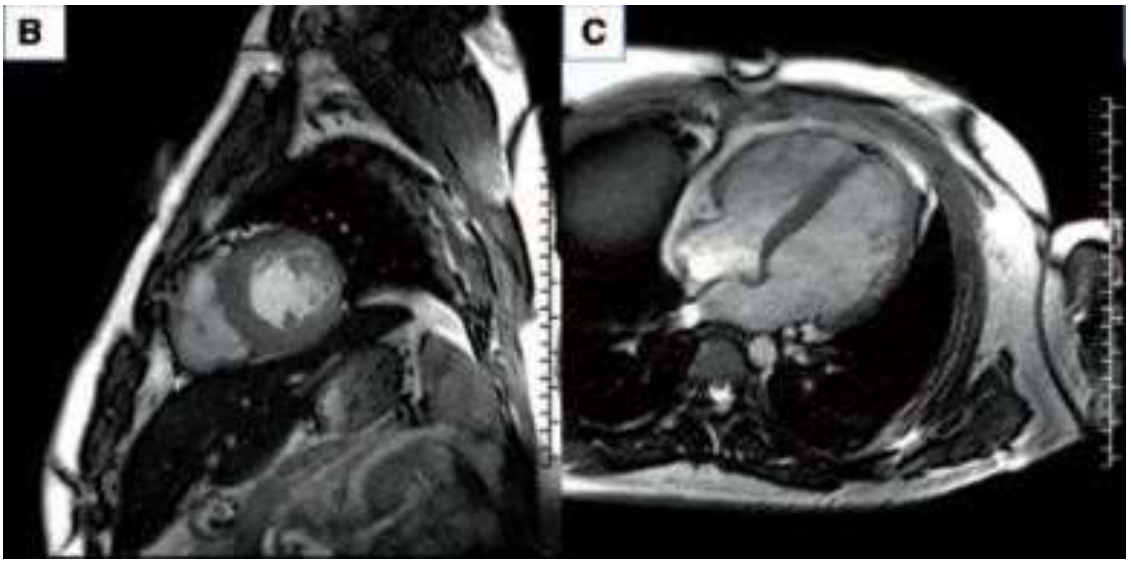
Ataxia is diminished. Another characteristic that is evident in these patients is the presence of fibrosis of the cardiac tissue, which is corroborated by the concomitant thinning of the left ventricle in advanced stages, which leads to the conclusion that this fibrosis is a common feature of these patients during the progression of this disease (16).

Cardiac MRI, with evidence of ejection fraction of 45% and mild asymmetric septal hypertrophy (17).



Source: Cardiomyopathy in Friedreich's Ataxia. Salazar P, Indorkar R, Dietrich M, Farzaneh-Far A. Eur Heart J. 2018;39(7):631

Treatment

Disease-Modifying Therapies

Clinical trials have focused on treating frataxin deficiency, specifically considering its role in oxidative stress and iron accumulation in Friedreich's Ataxia; therefore, antioxidants and iron chelating agents have been used and evaluated for use in monotherapy and in combination, with inconsistent results. There are other drugs that are based on ameliorating frataxin deficiency, e.g. histone deacetylase inhibitor, which is a promising therapeutic strategy.

A trial with nicotinamide, a class III histone deacetylase inhibitor, has shown sustained increases in frataxin levels in patients with Friedreich's Ataxia. The moTreatment for cardiac symptomatology depends on the presenting condition. It should always be remembered that the use of negative inotropic or pro-arrhythmic drugs is prohibited, because the heart is structurally impaired or even in heart failure. The decision to use anticoagulants should be based on the CHA2DS2VASc2 score. Supportive therapy is not necessary in patients with normal ejection fraction or no signs and symptoms of heart failure. If the patient has baseline heart failure and decreased ejection fraction, treatment should be initiated.

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and a beta-blocker are suggested, as their use results in reduced mortality and hospitalization. If they present symptoms of heart failure, diuretics should be added, such as mineralocorticoid receptor antagonists, especially if there is a decrease in ejection fraction of less than 35% and the NYHA scale is III or IV. Digoxin may be considered depending on symptomatology and ejection fraction. Patients with ejection fraction less than 35%, electrocardiogram with QRS greater than 0.12 seconds, and sinus rhythm, device therapy such as cardiac resynchronisation therapy should be considered (19)(20).

CONCLUSIONS

Friedreich's Ataxia is a neurodegenerative pathology with a genetic aetiological component that affects cells at the molecular level, leading to neurological alterations; however, the alterations are not only focused on the nervous system, but also affect the heart; therefore, it is necessary to take into account that these patients should always be monitored at a multidisciplinary level, especially at the cardiovascular level; this is vital, because patients with advanced progression of the disease, usually manifest mainly cardiovascular problems.

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