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FRIEDREICH'S ATAXIA: CLINICAL AND THERAPEUTIC PERSPECTIVES

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Abstract: Objective: The study aims to consolidate current knowledge on the etiological, clinical and therapeutic aspects of ‘s Ataxia Friedreichand present future perspectives for its diagnosis and treatment. **Methodology:** A narrative bibliographic review based on the PVO (Population, Variables and Outcome) strategy analyzed 21 articles selected from the databasePubMed, considering publications in English or Spanish from 5 to 10 years ago. **Results:**Non-drug treatment of ‘s Ataxia Friedreichincludes physiotherapy and occupational therapy, while antioxidants such as coenzyme Q10, Idebenone and EPI-743 aim to improve mitochondrial function. Omaveloxolone has shown benefits in neurological tests and quality of life. Genetic therapies are showing promise, with a focus on removing the GAA repeat or replacing frataxin. Deferiprone is used to reduce iron accumulation and slow neurodegeneration. New approaches include the drug Nomlabofusp, which seeks to correct mitochondrial deficiency, and studies investigating the use of viral vectors for gene therapy. Calcitriol increases levelsfrataxin, but does not show significant improvements in neurological symptoms, highlighting the need for further research. **Conclusion:** Despite the challenges in diagnosing and managing ‘s AtaxiaFriedreich, progress has been made with multidisciplinary support treatments and effective drug therapies. Genetic and epigenetic therapies are emerging as promising alternatives, with the tract corticospinal standing out as a therapeutic target in advanced stages of the disease.

Keywords: Friedreich’s Ataxia, Neurodegenerative Diseases, Hereditary Disorders,, Therapeutic Approach.Frataxin

INTRODUCTION

Hereditary cerebellar ataxias (ICAs) form a heterogeneous group of rare neurodegenerative diseases that predominantly affect the cerebellum, with frequent involvement of the spinal cord and peripheral nerves. These conditions are characterized by a progressive cerebellar syndrome, which often results in significant disabilities. It is estimated that the combined prevalence of ICAs is approximately 1:10,000, making these diseases a common reason for consultations at centersneurogenetics . In recent decades, technological advances, especially next-generation sequencing (NGS), have made it possible to identify more than 100 new genetic entities related to ICAs and up to 500 genes associated with clinical conditions that include cerebellar ataxia. This expansion in knowledge requires periodic bibliographic reviews to consolidate data and guide clinical practices, especially in the diagnosis and treatment of these conditions(1).

Among the ICAs, 's Ataxia stands out as Friedreich(FRDA) the most common hereditary form of autosomal recessive ataxia, with an estimated incidence of 1 in 50,000 individuals in Caucasian populations. FRDA is mostly caused by expansions of biallelic the GAA in trinucleotide intron 1 of the FXN gene, located on chromosome 9. This mutation results in a deficiency of the mitochondrial protein frataxin, which is essential for iron homeostasis, biosynthesis of iron-sulphur (clusters Fe-S) and maintenance of mitochondrial function. Reduced levels frataxin lead to severe metabolic dysfunction, increased oxidative stress and impairment of the central and peripheral nervous system. The first clinical signs include progressive ataxia, dysarthria and scoliosis, often accompanied by cardiac manifestations such as hypertrophic cardiomyopathy, which represents the main cause of mortality in patients with FRDA (2,3).

ARF is a complex condition that can also present endocrine, orthopedic and cardiac complications, amplifying the impact of the disease on patients' quality of life. Although cardiac manifestations are widely recognized as a critical complication of the disease, studies indicate that recommended cardiac assessments are not carried out regularly in a significant proportion of patients, particularly in regions with limited resources, highlighting gaps in clinical management (4).

Recent advances in the study of FRDA have focused on innovative therapeutic interventions, such as activation of the NRF2 pathway, strategies for restoring levels frataxin and gene editing techniques. In addition, new insights into the transcriptional and post-transcriptional regulation of frataxin have brought promising implications for the development of targeted therapies. These approaches offer hope for better modification of the course of the disease and an improvement in patients' quality of life (5,3).

Given the significant advances in the understanding of FRDA and the growing recognition of its clinical and genetic complexity, this literature review seeks to consolidate current knowledge on the etiological, clinical and therapeutic aspects of the disease. By integrating these findings, the aim is not only to highlight existing gaps in the literature, but also to propose future directions for the diagnosis and management of this debilitating hereditary ataxia.

METHODOLOGY

This study consists of a narrative literature review developed according to the criteria of the strategy**PVO,** which stands for: Population or research problem, variables and outcome. It was used to prepare the work through its guiding question: **What are the clinical and therapeutic perspectives addressed in Friederich's ataxia**

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The searches were carried out in the database PubMed using the Health Sciences Descriptors (DeCS). The following descriptors were used in different combinations with the Boolean term "AND": Friedreich's ataxia, Neurodegenerative diseases, Hereditary disorders, Frataxin/Frataxin, Therapeutic approach. From this search, a total of 33 articles were found, which were then submitted to the selection criteria.

The inclusion criteria were: articles published in English and Spanish, published in a period of 5 to a maximum of 10 years and which addressed the objectives proposed for this study. The exclusion criteria were: duplicate articles, articles in abstract form or articles that did not address the objectives and other inclusion criteria. After applying the inclusion and exclusion criteria, 21 studies were selected for this study.

RESULTS

The main pathological basis of is the deficiency of the proteinFriedreich's ataxia frataxin, which causes a decrease in ATP and oxidative damage in the cells of the central and peripheral nervous system. This disease is autosomal recessive, causing progressive neurodegeneration that varies according to the genetic and epigenetic factors of the individuals. The clinical picture is based on progressive gait ataxia, with proprioceptive sensory impairment, as well as other symptoms such as limb atrophy, loss of muscle tone, spasticity, cerebellar dysarthria and non-neurological symptoms, including complex disorders, cardiovascular disorders and the development of diabetes, causing significant social and occupational damage. Being more common in Caucasians, FRDA has an incidence of 1 in every 30-50,000 people worldwide(5).oculomotor

The discovery of new therapeutic targets has been essential for a promising advance in the evolution of the disease. The non-drug therapies offered to patients with 's ataxia Friedrerichare: physiotherapy, speech therapy and occupational therapy, with broad support for dysarthria, dysphagia, psychological support, gait improvement, among others. With an emphasis on improving mitochondrial function, antioxidants have been studied, such as analogues of coenzyme Q10, which studies estimate that 50% of FRDA patients use coenzyme, although studies on therapeutic efficacy are lacking. As well as others such as Idebenone and EPI-743(2).

A meta-analysis evaluated the effect of interventions targeting mitochondrial function, frataxin and clinical symptoms in 1409 patients with 's ataxiaFriedreich. Among the 43 studies analyzed, a statistically significant improvement in 's Ataxia Rating Scale scores was observed Friedreich(FARS and mFARS) in 205 patients after 15 months of treatment with drugs that increase mitochondrial function, especially omaveloxolone. However, this evidence was of very low quality. In addition, ten studies, mostly observational, with 261 patients suggested benefits in the measurement of left ventricular mass (LVMI) after 28.5 months of treatment, with the drugs being the idebenone and deferiprone most prominent. However, there were no significant changes in other biomarkers, such as clinical or neurophysiological, not even over the natural course of the disease(6).

FRDA can be treated in two ways: reversing the condition caused by protein deficiency frataxin (genetic and epigenetic therapies, protein replacement, FXN reversal and silencing) and also improving coexisting pathogenic events. Among the treatments, Omaveloxolone and Dimethyl Fumarate activate genes that protect cells from oxidative damage, increasing NRF2 levels and preventing its degradation. Benefits have been seen in neurological tests of patients taking Omaveloxolone, as well as correction of abnormal lipid metabolism and reversal of intrinsic biomarkers of ADRF, leading to an improvement in patients' quality of life(5).

Genetic therapies involving gene silencing have also demonstrated therapeutic advances. The sustained restoration of frataxin, if carried out under optimal time and conditions, is a promising treatment on a scientific level. Removal of the GAA repeat sequence or transfection of the frataxin cDNA causes restoration of cellular properties. This restoration can also be done directly with protein or with gene replacement. In addition, advantages such as improvements in all tissues of the body make gene therapy highly effective, but with restrictions on dosage, onset time, duration and efficacy. Gene regulation at different stages, such as transcriptional, post-transcriptional and post-translational, opens up different possibilities for therapeutic targets(8,5).

In view of the accumulation of iron in the tissues caused by reduced levels of frataxin and the consequent interruption in the assembly of the Fe-S cluster (iron and sulphur), therapies with Deferiprone, which is an iron chelator, have been used to reduce this accumulation in the brain and muscles, with the intention that the decrease in iron will delay neurodegeneration. The use of DFO also improves the distribution of iron between the cytosol and mitochondria, but it should be used with caution, as low doses improve cardiac parameters, but high doses decrease levels frataxin and enzyme activityFe-S (9,3).

Furthermore, most therapeutic targets are found in specific regions of the CNS. Drugs can be used directly in the brain parenchyma by application in the cerebrospinal fluid, as well as others that have mechanisms of action capable of crossing the blood-brain barrier. The choice of therapeutic targets depends on the patient's age, time of progression and the desired goal according to the clinic, but the proprioceptive system is considered the main target for restorationfrataxin (10,11).

Another innovative therapy is the drug Nomlabofusp, which is a recombinant fusion protein designed to overcome deficiency frataxin in cells. It has a structure that combines with a cationic peptide and enables to enter frataxin cells. In addition, the mitochondrial targeting sequence ensures that it is transported correctly to the inside of the mitochondria. This therapy has the potential to correct the central mitochondrial deficiency of the disease by addressing its underlying cause. Initial clinical studies are investigating the safety, pharmacokinetics and pharmacodynamics of nomlabofusp, yet it could represent a significant advance in the treatment of 's ataxiaFriedreich, offering a specific and targeted approach to the underlying cause of the disease(12,2).

Other studies investigate the efficacy and tolerability of histone inhibitorsmethyltransferase (HMTase), BIX0194 (G9a inhibitor) and GSK126 (EZH2 inhibitor), to specifically target and reduce the levels of histone modifications in fibroblasts. The results showed that the combination of BIX0194 and GSK126 significantly increased FXN gene expression and reduced repressive histone marks. However, an increase in protein levels was not observedfrataxin . Furthermore, they encourage the investigation of inhibitors HMTase with other epigenetic therapies(13).

In addition, another paper reviews the use of viral vectors, especially viruses adeno-associated (AAVs), in gene therapy for neurodegenerative diseases such as 's AtaxiaFriedreich. AAVs, in particular serotypes 9 and rh10, are promising due to their ability to cross the blood-brain barrier, low initial immune response and efficiency in neuronal cells. The administration of frataxin (FXN) and factor brain-derived (BDNF) by these vectors has been shown to be effective in models of FA, but the neurotrophic immunotoxicity and phenotoxicity associated with the overexpression of these proteins highlight the need to optimize the dose, vector design and delivery route. The systemic intravenous route, although less efficient in the central nervous system (CNS), is widely used due to its low

invasiveness. In addition, the YG8JR mouse model, which carries a human version of frataxin with 800 GAA repeats, has emerged as a relevant animal model for evaluating new therapies for AF(14).

In addition, calcitriol, when administered at a minimum dose of 0.25 mcg/24h, has been shown to increase levels frataxin in patients with (FRDA), with minimal side effects. However, the lack of significant improvement in neurological symptoms highlights the complexity of the disease's progression. Previous studies with cell models suggest that calcitriol may have a beneficial effect on mitochondrial function and oxidative stress parameters. Clinical trials using higher doses of calcitriol, such as 0.50 mcg daily, as well as a larger cohort of patients and/or treatmentsprolonged, may be essential for future interventions. These studies would help to confirm whether the increase in levels frataxin is sustained over time and whether it can slow down the progression of the disease after one year of treatment(15).

DISCUSSION

Friedreich's Ataxia (FRDA) is a progressive neurodegenerative disease of autosomal recessive genetic origin, characterized by a deficiency of frataxin, a protein essential for mitochondrial function. The lack of this protein results in oxidative damage and impairment of the cells' energy metabolism, with particularly severe effects on the central nervous system (CNS) and peripheral nervous system. The clinical picture is characterized by progressive ataxia, proprioceptive impairment, muscle disorders, spasticity and a series of manifestationsextracerebral, such as cardiovascular disorders and diabetes (15).

Given the significant impact of FRDA on patients' quality of life, there has been an intense search for therapies that can halt or slow down the progression of the disease. The therapeutic approach can be divided into two broad groups: treatments reversing deficiency aimed at and treatments aimed at improving coexisting pathological events, such as iron accumulation. Non-drug therapy, including physiotherapy, speech therapy and occupational therapy, remains fundamental to improvingfrataxin quality of life, especially in controlling dysarthria and maintaining mobility (16).

More recent efforts have focused on modulating mitochondrial function, given its importance for the pathophysiology of the disease. Omaveloxolone, a drug that increases mitochondrial function, has shown promising results in clinical trials, with improvement in 's Ataxia Rating Scale scores Friedreich(FARS and mFARS) (article 5 of the original). However, the evidence is still of low quality, with more studies needed to validate the long-term therapeutic effects (17).

In addition, the use of iron chelators, such as deferiprone, has been explored to reduce the accumulation of iron in the mitochondria and brain, thus slowing neurodegeneration (article 21 of the original). However, it is important to note that the use of these drugs must be carefully monitored, as high doses can result in adverse effects, such as decreased activity of the enzyme Fe-S and frataxin (18).

Innovative treatments, such as gene therapies, have also shown significant potential. Sustained restoration of frataxin, either by gene silencing or gene replacement techniques, has been considered a promising approach (19). Recent studies have shown that using viral vectors to deliver the FXN gene directly into neuronal cells is a strategy that can overcome the current limitations of gene therapy, although challenges in terms of immunotoxicity and efficiency still need to be resolved (20).

In addition, more specific treatments, such as the use of calcitriol, have shown an increase in levelsfrataxin, but clinical improvement has been limited. This reflects the complexity of the disease and the need for more effective interventions. Histone inhibitors methyltransferase have also been explored, with some

studies showing that they can increase FXN gene expression, although an improvement in protein production has not yet been observed frataxin (21).

Finally, the development of specific therapies such as Nomlabofusp, a recombinant fusion protein to overcome deficiencyfrataxin, and interventions to optimize delivery frataxin by viral vectors are promising. These approaches aim to correct mitochondrial deficiency in a more effective and targeted way, with the potential to represent a significant advance in the treatment of the disease (15).

CONCLUSION

The pathogenesis of ‘s Ataxia Friedreichis complex, while the early loss of proprioceptive afferents remains a characteristic aspect of the pathology, other areas such as metabolic consequences, the system corticospinal and the cardiac system are affected by the neurological disorder. Despite the challenges in early diagnosis and management of the disease, significant advances in understanding the pathophysiology and treatment have been gaining ground, such as supportive treatment with speech therapy, physiotherapy, drug therapy such as the use of Omaveloxolone,Deferiprone, Nomlabofusp and itself, Calcitriol have shown benefits in clinical trials, while genetic and epigenetic therapies are emerging as promising alternatives to modify the course of the disease.

The proprioceptive system, generally considered a primary target for treatment restore mitochondrial function and toregulate frataxin expression, shows substantial evidence of hypoplasia and/or early developmental loss, with minimal evidence of progression over time. On critical analysis, it seems likely that this system is not an ideal target for therapies administered after early childhood, so targeting DN of the cerebellum is likely to be most effective early in the course of the disease, when it is functionally affected but still shows limited atrophy. Thetract, on the other hand corticospinal, degenerates over time, contributing to the progression of the disease throughout its final stages and can be considered a target.

This study analyzed in detail the clinical, epidemiological and therapeutic implications of FRDA, and it is clear from the analysis of the data presented that a multidisciplinary approach and the implementation of preventive strategies are important. Although there is no definitive cure for the disease, the continuous progress in translational and clinical research reinforces the possibility of more effective therapies in the future, combined with multidisciplinary strategies and a combination of personalized treatments, which will offer a better quality of life to patients and achieve the goal of slowing down the progression of the disease. In view of this, the need for new clinical studies and the expansion of access to experimental treatments are fundamental for progress in the treatment of ‘s AtaxiaFriedreich.

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