REVIEW ARTICLE

FRIEDREICH ATAXIA: GENETIC INSIGHTS, PATHOPHYSIOLOGY, AND EMERGING THERAPEUTIC STRATEGIES

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Abstract:

Friedreich's ataxia is a rare, inherited autosomal recessive neurodegenerative disorder that primarily affects the nervous system, causing progressive damage to the spinal cord, peripheral nerves, and cerebellum, leading to impaired muscle coordination. Most patients have homozygous GAA expansions in the first intron of the frataxin gene on chromosome 9, causing epigenetic changes that reduce frataxin expression. This gene mutations as a mitochondrial protein, its deficiency leads to mitochondrial iron overload, impaired energy production, and increased reactive oxygen species. Neurological degeneration, particularly in sensory and cerebellar pathways, is compounded by cardiac hypertrophy and metabolic disturbances, making FRDA a devastating multisystem disorder. A multidisciplinary diagnostic approach is followed. Genetic testing remains the gold standard, complemented by imaging, electrophysiological, and histological studies. Clinical rating scales provide an objective measure of disease severity, aiding in both diagnosis and disease monitoring. There is no cure, but treatment focuses on symptom management. In 2023, the FDA approved Omaveloxolone, the first treatment to help improve motor function by reducing oxidative stress. Emerging therapeutic strategies, including gene therapy and frataxin-targeted approaches, offer potential disease-modifying treatments. The present review focuses on the genetic basis, pathophysiology, clinical symptoms, diagnosis, differential diagnosis and treatment strategies for Friedreich's ataxia.

Keyword: Friedreich's Ataxia; Neurodegenerative Disorder; Omaveloxolone.

Introduction:

First described by Nikolaus Friedreich in 1863, Friedreich's ataxia (FRDA) is a rare, inherited, autosomal recessive neurodegenerative disorder that primarily affects the nervous system, causing progressive damage to the spinal cord, peripheral nerves, and cerebellum, leading to impaired muscle coordination (ataxia). It is the most common autosomal recessive ataxia, accounting for over 50% of hereditary ataxia cases. FRDA typically begins around puberty with progressive limb and gait ataxia, dysarthria, loss of joint position and vibration senses, absent tendon reflexes in the legs, and extensor plantar responses. Non-neurological features include cardiomyopathy, diabetes mellitus, and skeletal deformities such as scoliosis and pes cavus. In 96% of cases, FRDA is caused by homozygous GAA triplet expansions in the frataxin (FXN) gene, while 4% have one expansion and another mutation. The length of the shorter GAA repeat inversely correlates with disease onset, severity, and progression rate. [1-2]

Epidemiology:

FRDA is an inherited ataxia that affects Indo-European populations and is the most prevalent inherited ataxia globally, affecting approximately 1 in 40,000 people with European descent. It is more common in Western Europeans and affects approximately 50% of all ataxia cases and 75% in patients under 25 years of age. The carrier prevalence is estimated to be 1 in 75, and it affects males and females equally. It frequently occurs in Europe, the Middle East, South Asia, and North Africa. FRDA is more common in northern Spain, Ireland, and France, but rare in Russia and Scandinavia. The disease is more prevalent in the White population than any other race, as the mutation is thought to originate from a common European ancestor. In East Asia (China, Japan, Korea and Southeast Asia), sub-Saharan Africa, and Amerindians the disease has never been reported in the indigenous populations. The onset usually occurs in early adolescence, with the age of onset typically between 8 years and 15 years. [3]

Clinical Symptoms:

Friedreich ataxia is a neurodegenerative disorder that typically manifests in childhood or early adulthood, with the average age of onset ranging from 10 to 15 years, although it can appear as early as two years old or even later into adulthood. The hallmark of FRDA is progressive ataxia, which initially affects gait and balance. This poor coordination and difficulty in maintaining posture worsen over time, with affected individuals often requiring assistance for mobility within a few years. In addition to gait ataxia, patients may develop slurred speech, referred to as dysarthria, and upper-limb ataxia, making fine motor tasks increasingly difficult. Early sensory impairment, including the loss of proprioception and diminished vibration sense in the lower limbs, is also commonly observed. Over the course of disease progression, individuals exhibit a broad spectrum of neurologic and systemic manifestations, which ultimately lead to significant disability and a shortened lifespan. In terms of neurological features, individuals with FRDA often experience a mixed axonal peripheral neuropathy, which can be detected by nerve conduction studies, revealing a decrease in sensory nerve action potentials and abnormal central motor conduction times. Muscle weakness, which starts in the hip extensors and abductors, gradually progresses to involve distal limbs, with muscle wasting becoming evident as the disease advances. Pes cavus, a condition characterized by high arches in the feet, is seen in about 55% of

individuals but usually does not cause significant discomfort. Spasticity is also common, particularly in the lower limbs, and can result in contractures, equinovarus deformities, and further complications in mobility. The disease can also lead to scoliosis, with a majority of individuals showing curvature of the spine, requiring interventions like bracing or surgery. Beyond these motor issues, the disorder has a substantial impact on speech and swallowing, with dysphagia affecting up to 92% of individuals and often leading to respiratory complications such as aspiration pneumonia. Cardiovascular complications are another significant aspect of FRDA. Hypertrophic cardiomyopathy occurs in approximately two-thirds of affected individuals, often presenting later in the disease course but occasionally even before the onset of ataxia. This cardiomyopathy can lead to arrhythmias, congestive heart failure, and sudden cardiac death. The risk of mortality from cardiovascular complications increases with disease progression, with survival often limited to the fourth or fifth decade of life. In addition to these motor and cardiac issues, FRDA is associated with various systemic manifestations such as diabetes mellitus, which affects up to 30% of individuals, and hearing loss, which may manifest as sensorineural hearing loss or auditory neuropathy. Cognitive function in FRDA is typically preserved, although some individuals may experience slowed mental and motor reaction times and impairments in attention, executive function, and memory. Psychosocial aspects of the disease also include an increased tendency for certain personality traits, such as persistence and low self-transcendence, which can impact interpersonal relationships. Advances in neuroimaging have shown clear evidence of cerebral, cerebellar, and spinal cord involvement, with specific patterns of white and gray matter atrophy observed in the brain and spinal cord. In some individuals, structural changes in the dentate nucleus, brainstem, and cerebellar penduncles are early signs of disease progression. While FRDA is a debilitating and progressive condition, there is variability in the rate of progression, and survival into the sixth or seventh decades of life has been documented in some individuals. However, the average age of death remains in the late 30s, with cardiac and respiratory complications being the primary causes of death. Atypical forms of FRDA, such as late-onset FRDA (LOFA) and very late-onset FRDA (VLOFA), present with milder symptoms and slower disease progression, though they still result in significant disability over time. [4-5]

Genetics:

Friedreich's ataxia (FRDA) is primarily caused by a pathological GAA trinucleotide expansion in the first intron of the *FXN* gene, with 1–3% of cases involving a compound heterozygous expansion and point mutation or deletion. Normal chromosomes have fewer than ~40 repeats, while the pathological threshold is 70, with FRDA patients typically having 600–900 repeats. Heterozygous carriers, present in about 1 in 85 Europeans, remain healthy. The GAA expansion silences the *FXN* gene, leading to reduced frataxin protein levels. This silencing may result from transcriptional blockade by structures like 'sticky DNA' triplexes and R-loops or position effect variegation-like mechanisms, where GAA repeats induce heterochromatisation, rendering nearby genes inactive. Aberrant epigenetic changes, such as excessive DNA methylation and histone modifications, exacerbate gene silencing. DNA methylation upstream of the repeats correlates with reduced *FXN* expression and earlier disease onset, while histone modifications promote chromatin heterochromatisation around the expansion.

These epigenetic insights offer potential therapeutic strategies to restore *FXN* expression and mitigate FRDA pathogenesis. Further research is needed to identify specific chromatin modifiers responsible for gene silencing. [6]

Mitochondrial Implications:

FRDA is caused by mutations in the FXN gene, leading to reduced levels of frataxin, a mitochondrial protein critical for cellular functions. The most common mutation is a GAA trinucleotide expansion in the first intron of the FXN gene, causing transcriptional repression and frataxin deficiency. This deficiency disrupts mitochondrial functions, with wide-ranging effects on the peripheral and central nervous systems, heart, and pancreatic islets.

1. Iron Metabolism: Frataxin deficiency impairs iron–sulfur cluster (ISC) biogenesis, critical for mitochondrial enzymes, leading to mitochondrial iron overload and disrupted cellular iron homeostasis. This dysfunction contributes to oxidative stress and impaired energy production.
2. Energy Production and Oxidative Stress: Reduced frataxin levels impair oxidative phosphorylation (OXPHOS), decreasing ATP production and increasing reactive oxygen species (ROS), which disrupt cellular redox balance and contribute to oxidative damage.
3. Mitochondrial Quality Control: Frataxin deficiency impacts mitochondrial biogenesis and autophagy, with reduced capacity for energy adaptation. Dysregulated oxidative stress exacerbates mitochondrial damage, leading to apoptosis or necrosis in specific cell types, including neurons and pancreatic β cells.
4. Mitochondrial Network Dynamics: Frataxin depletion affects mitochondrial fusion, fission, and movement, disrupting axonal transport in neurons. The response to these changes varies by cell type and environmental factors.
5. Communication with Other Organelles: Impaired interaction between mitochondria and organelles like the endoplasmic reticulum disrupts calcium homeostasis, cytoskeletal organization, and neuronal function. [7-8]

Pathophysiology:

Friedreich's ataxia (FRDA) is an autosomal recessive neurodegenerative disorder caused by partial frataxin deficiency, typically due to GAA trinucleotide repeat expansions in the *FXN* gene. Some patients are compound heterozygotes with one expanded allele and a second allele carrying a different mutation, such as missense, nonsense, or splicing changes. Frataxin deficiency disrupts mitochondrial function, iron homeostasis, and oxidative stress management, leading to progressive degeneration in the nervous system, heart, and pancreas. The neurological manifestations, cardiac complications, and metabolic disruptions of FRDA reflect its complex pathophysiology and multisystem involvement.

Neurologically, FRDA is characterized by mixed sensory and cerebellar ataxia due to the degeneration of proprioceptive pathways in the peripheral nervous system, spinal cord, and cerebellum. Early involvement includes the dorsal root ganglia (DRG), where large sensory neurons responsible for proprioception and vibration sense are severely affected. Loss of these neurons results in the degeneration of large myelinated fibers in the DRG axons and dorsal root nerves, while unmyelinated fibers are largely spared. Satellite cells in the DRG form residual nodules composed of ferritin-positive

clusters of nuclei, reflecting abnormal iron metabolism. This iron dysregulation, seen in both sensory neurons and satellite cells, is a hallmark of FRDA and underscores the role of mitochondrial dysfunction. The degeneration of sensory pathways extends centrally to the dorsal columns, spinocerebellar tracts, and corticospinal tracts of the spinal cord, contributing to proprioceptive loss, muscle weakness, and spasticity. Furthermore, the gracile and cuneate nuclei, Clarke's column, and the dentate nucleus (DN) in the cerebellum are prominently affected, resulting in dysmetria, dysarthria, and dysphagia.

The cerebellum plays a critical role in FRDA pathophysiology, particularly the DN, which exhibits severe atrophy, neuronal loss, and iron accumulation. Histopathological studies show significant depletion of large DN neurons and abnormal glutamatergic and GABAergic signaling between the DN and Purkinje cells, disrupting motor coordination. However, Purkinje cells and their dendrites remain intact, suggesting selective vulnerability of specific neuronal populations. The altered iron metabolism in the cerebellum, coupled with the involvement of copper and zinc, further complicates the pathogenesis, although the precise mechanisms remain under investigation.

Peripheral sensory nerves in FRDA exhibit hypomyelination and axonal degeneration, predominantly affecting large-diameter fibers. Schwann cells, which form the myelin sheath, display reduced expression of S100α, suggesting a defect in Schwann cell-axon communication. Despite this, laminin 2 expression is preserved, albeit in an altered pattern. Hypomyelination, combined with axonal degeneration, likely results from disrupted mitochondrial bioenergetics and impaired intracellular signaling between Schwann cells and axons. This "dying-back" axonopathy originates distally and progresses proximally, exacerbating sensory deficits.

Cardiac complications are among the most life-threatening aspects of FRDA and are present in over 90% of patients, often preceding neurological symptoms. Hypertrophic cardiomyopathy, characterized by concentric or septal hypertrophy, interstitial fibrosis, and myocardial fiber degeneration, is a hallmark feature. Intracellular iron accumulation in cardiomyocytes contributes to mitochondrial damage, oxidative stress, and impaired contractility. Recent studies suggest that frataxin deficiency disrupts iron trafficking between mitochondria and the cytosol, leading to cytosolic iron deficiency despite mitochondrial iron overload. Additionally, lipid metabolism is impaired, as evidenced by hyperacetylation of mitochondrial proteins in cardiac tissues and inhibition of the SIRT3 pathway, which regulates fatty acid β-oxidation. These findings highlight the role of mitochondrial dysfunction in cardiac pathology and point to lipid homeostasis as a potential therapeutic target.

Metabolic complications, including diabetes mellitus and glucose intolerance, occur in 10–30% of FRDA patients. Diabetes in FRDA results from progressive β-cell loss in the pancreas due to bioenergetic deficits caused by mitochondrial dysfunction. Islets of Langerhans become smaller and undergo structural changes, contributing to reduced insulin secretion. The exact relationship between frataxin deficiency, mitochondrial dysfunction, and β-cell death requires further investigation but underscores the systemic impact of FRDA. [9-11]

Histopathological Findings:

Key findings include the loss of myelinated fibers in the dorsal columns and corticospinal tracts of the spinal cord, accompanied by compact fibrillary gliosis without inflammatory cells in these regions. There is significant degeneration and death of fibers within the dorsal columns and corticospinal tracts, resulting in their shrinkage and capsular cell proliferation. Large myelinated fibers are notably absent in the posterior roots, with a marked decrease in myelinated axons in peripheral nerves. The dorsal root ganglion exhibits neuronal destruction and atrophy, along with hypoplasia. Additionally, the Clarke column in the thoracic spinal cord shows degeneration and cell loss. The cerebellum is also affected, with progressive atrophy of large neurons in the dentate nucleus, patchy loss of Purkinje cells in the superior vermis, and neuronal loss in the inferior olivary, pontine, and medullary nuclei. Neuronal loss extends to the optic tracts, and there is an absence of Betz cells in the motor cortex. [12]

Diagnosis:

Friedreich ataxia is a hereditary neurodegenerative disorder that can be diagnosed through a combination of genetic, laboratory, imaging, and electrophysiological studies. Genetic counselling is available for prenatal diagnosis in families with a known history of FRDA, though population-wide carrier screening is not practical. A commercially available trinucleotide repeat expansion assay serves as the definitive diagnostic test for suspected cases. Laboratory studies indicate that while iron (Fe) and zinc (Zn) levels remain within normal ranges in FRDA patients, copper (Cu) levels are significantly reduced. Additionally, cerebrospinal fluid (CSF) analysis does not reveal any abnormalities in FRDA patients.

Imaging studies play a crucial role in evaluating FRDA -related neurodegeneration. Magnetic resonance imaging (MRI) is the preferred modality, consistently demonstrating atrophy of the cervical spinal cord with minimal cerebellar involvement. Transcranial sonography, an affordable and accessible technique, highlights dentate hyperechogenicity, a key feature of FRDA. Moreover, mass spectrometry assays are being developed to measure frataxin levels as a potential biomarker for disease progression. Cardiac assessments, such as echocardiography, frequently reveal symmetric, concentric ventricular hypertrophy, though some cases present with asymmetric septal hypertrophy. Electrocardiography (ECG) abnormalities are present in approximately 65% of FRDA patients, with common findings including T-wave inversions and ventricular hypertrophy.

Electrophysiological studies provide additional insights into FRDA. Nerve conduction velocity (NCV) studies often yield normal or mildly reduced velocities, while sensory nerve action potentials (SNAP) are absent in over 90% of cases. Confocal microscopy of the skin, used to evaluate Meissner's corpuscles and epidermal nerve fiber density, offers potential structural markers of sensory involvement. Brainstem auditory evoked responses in FRDA typically show absent waves III and IV while preserving wave I, indicating central auditory pathway involvement. Similarly, visual evoked potentials are abnormal in nearly two-thirds of FRDA patients, characterized by delayed latency and reduced P100 wave amplitude. Somatosensory evoked potentials (SSEP) reveal delayed central conduction, dispersed sensory cortical potentials, and impaired central motor conduction. Studies have

also suggested that deficits in spatial position sense (SPS) precede joint position sense (JPS) and vibration sense (VS), making SPS a more sensitive early diagnostic marker.

Histological findings further corroborate the neurodegenerative changes observed in FRDA. Examination of the lower cervical spinal cord shows myelin loss in the dorsal columns and corticospinal tracts, with milder involvement of spinocerebellar tracts. Affected areas exhibit compact fibrillary gliosis without significant macrophage activity, indicating slow degeneration. Dorsal spinal ganglia progressively shrink, leading to neuronal loss and capsular cell proliferation. Additionally, the posterior roots display a marked reduction in large myelinated fibers, and degeneration of Clarke's column neurons is evident within the thoracic spinal cord.

For clinical assessment, three validated scales are commonly used: the International Cooperative Ataxia Rating Scale (ICARS), the Friedreich Ataxia Rating Scale (FARS), and the Scale for the Assessment and Rating of Ataxia (SARA). The ICARS evaluates posture and gait disturbances, kinetic functions, speech disorders, and oculomotor abnormalities. Gait and standing balance tests help quantify ataxia severity, with scores ranging from normal to complete inability to walk. Limb coordination is assessed through tasks such as the heel-to-knee and finger-to-nose tests, where abnormalities in movement decomposition, intention tremor, and dysmetria are noted. Speech evaluation measures fluency and clarity, while oculomotor assessments examine gaze-evoked nystagmus, ocular pursuit, and saccadic dysmetria. These combined measures provide a comprehensive evaluation of disease progression and functional impairment in FRDA patients. [13]

Differential Diagnosis:

The differential diagnosis of Friedreich ataxia is complex due to its variability in morbidity and mortality. While the clinical presentation of typical FRDA is often distinct, early-stage cases and atypical forms may pose diagnostic challenges. Conditions that should be considered in the differential diagnosis include various ataxias, peripheral neuropathies, and spasticity disorders. Ataxic disorders such as spinocerebellar ataxias, episodic ataxia, and ataxia with vitamin E deficiency can mimic FRDA but are distinguished through genetic testing, imaging, or biochemical markers. Peripheral neuropathies like hereditary motor and sensory neuropathy, Charcot-Marie-Tooth disease variants, and chronic inflammatory demyelinating polyneuropathy may present similarly but differ in inheritance patterns and specific clinical features. Additionally, spastic ataxias, such as autosomal recessive spastic ataxia of Charlevoix-Saguenay and hereditary spastic paraplegia, can overlap with FRDA but show distinguishing MRI findings. Other conditions, including dentatorubro-pallidoluysian atrophy, abetalipoproteinemia, Refsum disease, and ataxia-telangiectasia, have unique genetic and biochemical markers that differentiate them from FRDA. Drug-induced ataxia should also be considered, as it resolves upon discontinuation of the causative agent. [14]

Management:

Frataxin, a protein with an unclear physiological function, plays a key role in regulating mitochondrial iron transport and the synthesis of iron-sulfur cluster-containing enzymes. Mutations in the frataxin gene lead to deficiencies in iron-sulfur clusters in mitochondrial electron transport

complexes I, II, and III, as well as aconitase. This results in mitochondrial dysfunction and possibly the generation of reactive oxygen species (ROS), contributing to the disease's progression. [15]

Treatment strategies targeting mitochondrial dysfunction include mitochondrial enhancers, free radical scavengers, and iron chelators. Notable treatments for FRDA are: [16]

- **Omaveloxolone:** It is an Nrf2 activator used as a targeted treatment for Friedreich ataxia. The specific mechanism of action is not fully understood, but it is believed to enhance mitochondrial function and reduce oxidative stress, which is a key pathological feature of the disease. Omaveloxolone was approved for medical use in the United States in February 2023 and in the European Union in February 2024 to address the underlying mitochondrial dysfunction in FRDA
- **Coenzyme Q10 and Vitamin E:** This combination of antioxidants addresses mitochondrial impairment and oxidative stress in FRDA. A study treating 10 patients with 2,100 IU of vitamin E and 400 mg of CoQ10 daily for six months showed improved cardiac and skeletal muscle bioenergetics. These improvements were sustained over 47 months. Echocardiography revealed increased cardiac function, as indicated by improved fractional shortening. While some physical function scores continued to worsen, bioenergetics and cardiac outcomes were notably better compared to untreated patients.
- **Idebenone:** A coenzyme Q10 analog, idebenone has been tested in several clinical trials. Studies at doses of 5 mg/kg per day showed reductions in cardiac hypertrophy. However, results were mixed, with one double-blind trial at 360 mg per day yielding negative results, possibly due to the short study duration (1.5 months). Longer trials (4-84 months) revealed improved cardiac function, but results varied, with some studies showing a reduction in left ventricular mass but worsening ejection fraction.
- **L-Carnitine:** A placebo-controlled trial with 3g of l-carnitine per day for four months demonstrated improvements in bioenergetics as measured by 31P-magnetic resonance spectroscopy. However, no significant changes were observed in ataxia ratings or echocardiographic parameters, suggesting that while bioenergetics may improve, motor function and cardiac outcomes remain unaffected.
- **Iron Chelation:** Deferiprone, an iron chelator capable of crossing cell membranes, showed promise in a phase II clinical trial by reducing iron content in the dentate nucleus, which is involved in the pathology of FRDA. This reduction was confirmed by decreased 1H-relaxation rates on MRI scans, indicating a potential role for iron chelation in managing iron accumulation in the mitochondria, a key feature of FRDA.
- **Stem Cell Therapy:** Currently, stem cell treatments for FRDA are not viable due to a lack of preclinical data and significant challenges in delivery, differentiation, and integration of new cells into the existing neuronal network.
- **Increasing Frataxin Expression:** Research is focusing on ways to increase frataxin expression, which is deficient in FRDA patients. Erythropoietin has shown a slight increase in frataxin expression in an initial clinical study, but it can lead to adverse effects, including an

increased risk of thrombosis. Another promising avenue involves histone deacetylase inhibitors, which have restored frataxin expression in cultured cells and transgenic mouse models. However, the safety and toxicity profiles of these inhibitors need further evaluation.

- **Other Potential Therapies:** The use of acetylcarnitine (2g per day) resulted in mild coordination improvements in a placebo-controlled trial, but its benefits were limited. Treatments like creatine and high doses of vitamin E have shown limited or adverse effects, with the latter linked to increased all-cause mortality in meta-analyses. Iron supplementation to treat anemia is discouraged, as it exacerbates mitochondrial iron overload and impairs frataxin expression, further worsening cellular function.

Cardiac symptoms in Friedreich ataxia (FRDA), particularly cardiomyopathy, are common in individuals with early-onset FRDA and can be life-threatening. Therefore, all patients diagnosed with FRDA should be referred to a cardiologist for regular evaluation and monitoring of heart function. Idebenone, at doses of 5-10 mg/kg per day, has been shown in several trials to potentially reduce left ventricular mass index and may improve heart function. The management of heart failure in FRDA follows standard protocols, including the use of diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers, aldosterone antagonists, and digoxin, with careful consideration of any contraindications. Heart failure in FRDA is often linked to a poor long-term prognosis. Cardiomyopathy can also lead to arrhythmias, primarily supraventricular, for which amiodarone, propafenone, or the implantation of a pacemaker may be considered as treatment options. Regular cardiac monitoring is crucial to managing these symptoms and ensuring timely intervention to improve outcomes for patients with FRDA.

Treatment interventions for diabetes mellitus in patients with Friedreich ataxia (FRDA) include a combination of weight monitoring, dietary recommendations, and hypoglycemic oral therapy.

Rehabilitation Therapy:

In Friedreich ataxia, patients typically experience progressive impairments in motor function and sensory integrity due to central nervous system disorders. These impairments are characterized by muscle weakness, particularly in the pelvis and lower extremities, with less involvement in the trunk and upper extremities. Orthopedic interventions are commonly used to address musculoskeletal issues. For example, spinal fusion with modern segmental constructs has proven effective in correcting hyperkyphosis during surgery, with the correction maintained postoperatively. However, methods like bracing or electrospinal instrumentation are less effective. Foot deformities can be managed with splinting, botulinum toxin injections, or surgery, depending on the severity of equinovarus. In some cases, orthopedic shoes may also provide some benefit.

To manage spasticity, physical therapy is recommended, which includes stretching programs, standing frames, and splints, alongside pharmacological treatments like baclofen and botulinum toxin. Adaptive equipment such as prostheses, walking aids, or wheelchairs can help maintain an active lifestyle. In the early stages of FRDA, walking aids can reduce falls, but their effectiveness may decline in the later stages, where they may compromise ambulatory safety. For more mobility, a power scooter can assist with community transport, while a manual wheelchair should be used in the patient's home

environment if needed. These interventions aim to improve mobility and quality of life for patients as the disease progresses.

Dysphagia management involves dietary modifications and, in later stages, the use of nasogastric or gastrostomy feeding. This should be managed by a multidisciplinary team including a speech-language therapist and dietitian. Some studies have indicated that muscle-strengthening exercises might help improve swallowing function, similar to findings in patients with Parkinson's disease.

Regarding bladder and sexual function, sphincter disturbances are common, affecting up to 40% of patients with FRDA. Oxybutynin, an anticholinergic, may help manage bladder overactivity. A urodynamic evaluation is recommended before treatment. Sexual dysfunction, especially in males, may also require symptomatic treatment.

Cognitive and mood disturbances are often present in FRDA, with slowed information processing and emotional disturbances like irritability, depression, and social isolation. Early-stage psychological support is crucial, particularly as the disease progresses and independence is lost. Selective serotonin reuptake inhibitors (SSRIs) are preferred for managing depression over tricyclic antidepressants, as SSRIs have a safer side effect profile. The use of L-tryptophan is discouraged due to the potential for serotonergic syndrome and lack of effectiveness for motor symptoms.

Prognosis:

Friedreich ataxia progresses differently in individuals, with earlier onset and longer GAA triplet expansions generally leading to more severe symptoms. The prognosis is poor, with most patients becoming wheelchair-bound by the age of 45 and the disease typically lasting 15 to 20 years. Cardiac dysfunction, particularly congestive heart failure and arrhythmias, is the leading cause of death, accounting for two-thirds of fatalities. While the average age of death is 36.5 years, it can range from 12 to 87 years, though some individuals with milder symptoms may live into their 60s or beyond. [17]

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