# SPINOCEREBELLAR DEGENERATION (FRIEDREICH ATAXIA)

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***Abstract:*** *Friedreich ataxia is a rare autosomal recessive hereditary disorder. The mutated gene is localized in the proximal long arm of chromosome 9. It is characterized by progressive degeneration of the spinocerebelar, corticospinal and posterior columns of the spinal cord. The typical age of onset is between 5 and 15 years. Clinically, it is characterized by gait ataxia, pyramidal syndrome, sensitive syndrome, the reflexes are modified, trophic, psychic and cardiac changes occur. Ataxia is of mixed cerebellar and sensory type. Later in illness, gait is possible only with bilateral support. The characteristic foot deformity takes the form of high plantar arch with retraction of the toes at the metatarsophalangeal joints and flexion at the interphalangeal joints. Later, dilated cardiomyopathy could be found. The evolution is slow progressive, the death is due to cardiac arrhythmia and congestive heart failure. Specific treatment does not exist. Idebenone, an antioxidant, reduces the progression of the left ventricular hypertrophy.*

***Keywords:*** *spinocerebellar degeneration, inherited ataxia, frataxina, hypertrofic cardiomyopathy*

***Rezumat:*** *Ataxia Friedreich este o boala rară cu transmitere autosomal recesivă. Se datorează alterării unei gene specifice localizată pe braţul lung al cromozomului 9. Este caracterizată printr-o degenerare progresivă a fibrelor spinocerebeloase, corticospinale şi a cordoanelor medulare posterioare. Debutează de obicei între 5 şi 15 ani. Tabloul clinic constă în ataxia mersului, sindrom bipiramidal, sindrom senzitiv, ROT modificate, tulburări trofice, psihice şi manifestări cardiace. Mersul este ataxic datorită afectării concomitente a cerebelului şi a sensibilităţii profunde. În stadiile tardive mersul devine posibil doar cu sprijin bilateral. Apare "piciorul Friedreich" (pes cavus) cu boltă plantară scobită şi degete "în ciocan". În stadiile severe se întâlneşte cardiomiopatia dilatativă. Evoluţia este lent progresivă, decesul survenind prin tulburări de ritm cardiac sau insuficienţă cardiacă congestivă. Nu există un tratament specific. Idebenone este un antioxidant cu efecte favorabile în cardiomiopatie*

***Cuvinte cheie:*** *degenerare spinocerebeloasă, ataxie ereditară, frataxina, cardiomiopatia hipertrofică*

## INTRODUCTION

Friedreich ataxia (FRDA) is a familial, progressive degeneration of the spinocerebellar and corticospinal tracts and the posterior columns, of autosomal recessive inheritance.(3)

Nicolaus Friedreich (1825-1882) – Professor of Medicine in Heidelberg, first described in 1863 this disease.(6)

FRDA is the most common of the early-onset hereditary ataxias in Caucasians, accounting for approximately 50% of all cases of hereditary ataxia. Most FRDA carriers and affected FRDA patients are believed to originate from a common European ancestor who lived more than 10,000 years ago. Frataxin gene expansions are therefore almost nonexistent among black African and Asian populations. It affects approximately 1 in 50.000 Caucasians. FRDA is an autosomal recessive trait, and thus no gender predilection is seen. The FRDA carrier rate has been estimated recently to be 1 in 60 to 1 in 90 with a disease prevalence of 1 per 29,000.(1,2,4)

The mutated gene in FRDA is localized in the proximal long arm of chromosome 9. The encoded protein is named frataxin. In adult humans, frataxin mRNA is most abundant in the heart and spinal cord, followed by liver, skeletal muscle, and pancreas. FRDA is caused by a unique mutation, the hyperexpansion of GAA triplet repeat in the first intron of the frataxin gene. Although GAA repeats in normal chromosomes consist of up to 40 triplets, disease-associated repeats contain from 70 to more than 1000 triplets. The consequence of the mutation is a reduction in levels of frataxin and loss of its function. Because the expansion size determines the level of residual frataxin expression, it has an influence on the severity of the phenotype. Differences in GAA expansion account for only about 50% of the variability in age of onset, indicating that other factors also influence the phenotype. A minimal residual level of functional frataxin is necessary to survive through embryonic development. To date, no other disease has been recognised as being caused by expansion of GAA triplet repeat.(4,5)

In eukaryotes, frataxin is encoded in nucleus, translated in cytoplasm, and then imported into mitochondria. Frataxin is an iron-binding protein which play an important role, not fully understand in mitochondrial metabolism. Frataxin has been shown to be involved in different aspects of intracellular iron metabolism, from biogenesis of heme and Fe-S clusters to

iron-binding storage and iron chaperone activity. Interaction with ferrochelatase, the enzyme that catalyses the final step of heme biosynthesis by inserting the ferrous ion into porphyrin. Frataxin, is involved in controlling cellular oxidative stress by reducing the production of reactive oxygen species. It was shown that frataxin protects DNA against iron-induced oxidative damage. Frataxins are small essential proteins whose deficiency causes a range of metabolic disturbances (6).

In patients with FRDA, abnormalities observed in dorsal root ganglia neurons are a primary event, whereas the neuronal loss in Clarke's column and the degeneration in the posterior column may be secondary events. Accumulation of lipofuscin, non-degradable intralysosomal substances originating from autophagocytosed cellular components has been reported from both the dorsal root ganglia and the cardiomyocytes of patients with FRDA.(7)

The typical age of onset is before 25 years, usually between 10 and 15 years. Ataxia of gait is nearly always the initial symptom. In some patients, kyphoscoliosis precede the neurological symptoms. Ataxia is of mixed cerebellar and sensory type. Truncal ataxia results in swaying and gait becomes broad-based, with frequent loss of balance. Limb ataxia causes increasing difficulty in activities requiring dexterity and precision such as writing and dressing. Ataxia is progressive and unremitting, although periods of stability are frequent at the beginning of the illness.(1,5)

Limb weakness of central origin appears and then worsens with the progression of FRDA. It initially affects proximal muscles, then becomes generalised and significantly contributes to disability. Amyotrophy occurs late in the illness.(1,2)

The cardiomyopathy is demonstrable in more than half of the patients. The myocardial fibres are hypertrophic and may contain iron-reactive granules. Shortness of breath and palpitations are the usual initial symptoms. The cardiomyopathy can develop insidiously but with fulminant consequences. In severe cases, the cardiomyopathy progresses to a dilatative stage with severe heart failure.(1,2,5)

Mentation has been preserved in all patients but emotional lability is frequent. Dysarthria consisting of slow, jerky speech with sudden utterances is almost universal. It usually begins within 2 years of disease onset and progresses until becomes almost unintelligible. Horizontal nystagmus may be present with the eyes in the primary position and is increased on lateral gaze. Rotatory and vertical nystagmus is rare. About 30% of patients develop optic atrophy. Ocular movements usually remain full, and pupillary reflexes are normal. 20% of patients develop sensorineural hearing loss with vertigo. The facial muscles may seem slightly weak. Dysphagia, particularly for liquids, is a feature of very advanced disease, for which eventually gastrostomy feedings are required. Sphincter control is usually preserved.(3,4)

The tendon reflexes are abolished in nearly every case. They may be obtainable when the patient is examined early in the illness. Plantar reflexes are extensor. The abdominal reflexes are usually retained until late in the illness. Loss of vibratory and position sense is invariable from the beginning. Later, there may be some diminution of tactile, pain, and temperature sensation. Some patients with more limited sensory neuronopathy retain reflexes and pyramidal involvement may lead to hyperreflexia and spasticity, to the point of mimicking a spastic paraplegia.(1,5)

About 10% of patients with FRDA develop diabetes mellitus and about 20% have carbohydrate intolerance. The characteristic foot deformity takes the form of a high plantar arch with retraction of the toes at the metatarsophalangeal joints and flexion at the interphalangeal joints (hammertoes). About 80 % of patients with FRDA have kyphoscoliosis that may cause pain and cardiorespiratory problems.(1,4,5)

There is no consistent abnormality of blood or CSF. Neurophysiological studies of the peripheral nervous system reveal a severe reduction or complete loss of sensory nerve action potentials with motor and sensory nerve conduction velocities within or just below the normal range. Visual evoked potentials are abnormal only in patients with associated optic atrophy. The chest and spine films show heart size and kyphoscoliosis. The electrocardiogram shows inverted T-waves in all patients with FRDA, ventricular hypertrophy in most, conduction disturbances in about 10% and supraventricular ectopic beats and atrial fibrillation occasionally. Echocardiography demonstrates concentric hypertrophy of the ventricles or asymmetrical septal hypertrophy. Structural neuroimaging by computer tomography and magnetic resonance imaging typically shows an atrophic cervical spinal cord.(4,5)

The rate of progression of Friedreich ataxia (FA) is variable. The disorder is progressive, with a mean duration of 15-20 years. More than 95% of patients are wheelchair bound by age 45 years. Commonly, patients survive to 25-30 years of age, although some patients have survived into the sixth and seventh decades, especially if they are free of heart disease and diabetes.(4)

There is no specific treatment. Standard treatment is administered for heart failure, arrhythmias, and diabetes mellitus. Apart from surgery for scoliosis and foot deformities that may be helpful in selected cases, no significant surgical treatment is available for FRDA. Orthopedic shoes improved gait disorders. Idebenone is a coenzyme Q analog that has antioxidant and oxidative-phosphorylation-stimulating properties. It has been shown in several trials to reduce the progression of left ventricular hypertrophy. Higher doses of idebenone were generally well tolerated and associated with improvement in neurologic function and ADL (activities of daily living) in patients with FRDA.(4)

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