Clinical Neurogenetics
Friedreich Ataxia

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KEYWORDS

• Friedreich ataxia • Triplet repeat expansion • Autosomal recessive • Mitochondria • Neurodegenerative disease

KEY POINTS

- Friedreich ataxia is the most common inherited ataxia in white people.
- Presentation is typically in adolescence, but can occur at any age.
- Signs and symptoms include posterior column and peripheral sensory neuropathy, areflexia, and ascending ataxia without cerebellar atrophy on brain magnetic resonance imaging, but less common phenotypes with preserved reflexes or progressive spastic paraplegia with less prominent ataxia also occur.
- Mortality is usually caused by cardiac morbidities, including arrhythmias or heart failure.
- Although there is no cure for Friedreich ataxia, management of comorbidities including scoliosis, dysphagia, sleep apnea, diabetes, cardiomyopathy, and arrhythmias can significantly improve quality of life and extend life expectancy.

INTRODUCTION

Definition

Friedreich ataxia is an autosomal recessive degenerative mitochondrial disorder affecting high-energy-use organs and tissues, including the heart and the central and peripheral nervous systems.[1] It is the most common cause of hereditary ataxia in the white population,[2] typically presenting in the first or second decade of life with slow progression.[3] In about 95% to 98% of affected individuals, the disease is caused by homozygous GAA TTC triplet repeat expansions in the first intron of the frataxin gene, *FXN*,[1] whereas point mutations or deletions in conjunction with an expanded triplet repeat account for the remainder of cases.[4,5] The expanded intronic alleles interfere with *FXN* transcription, decreasing the production of normally functioning frataxin protein to about 5% to 20% of normal.[6,7] Deficient frataxin levels result in excessive mitochondrial iron accumulation,[8,9] reduced iron-sulfur clusters vital for mitochondrial energy production,[10,11] and increased intracellular oxidative damage.[12–14] The consequence of these faulty cellular processes is inexorable cellular dysfunction, injury, and cell death producing the clinical phenotypes of this disease.[12,15] Treatments are supportive, and despite extensive ongoing research efforts there is currently no disease-modifying therapies or cure for Friedreich ataxia.

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SYMPTOMS AND CLINICAL COURSE

- Neurologic symptoms
  - Progressive gait instability and ataxia in 99% to 100% of patients, most often presenting in adolescence, resulting in loss of ambulation and unsupported sitting typically 10 to 15 years after onset of symptoms, although slower and faster progression are possible, and are related to repeat number and age of onset.[3,16–20]
  - Lower limb then upper limb incoordination and ataxia in 99% to 100% of patients.[3,16,18]
  - Weakness in feet and legs in 67% to 88% of patients,[3,16,19] followed in late disease by weakness in hands and arms.
  - Dysarthria typically early in the course, with slow, jerky speech, present in 91% to 97% of patients.[3,16,18,20]
  - Impaired sensation in feet in 73% to 92% of patients, followed by cool temperature and purple discoloration late in the course.[3,16,18–20]
  - Dysphagia in 27% to 64% of patients[16,19,20] worsening with advanced disease, particularly for thin liquids.
  - Impaired visual fixation and tracking.[20]
  - Decreased visual acuity in 13% to 27% of patients.[16,19]
  - Decreased hearing in 8% to 22% of patients.[3,16,19]
  - Urinary urgency then incontinence in late disease in 23% to 53% of patients.[16,18,19]
  - Preserved cognition, with mild executive dysfunction.[20]
  - Daytime fatigue caused by central sleep apnea.
- Cardiac symptoms
  - Palpitations caused by arrhythmias.[20]
  - Shortness of breath and exercise intolerance caused by hypertrophic cardiomyopathy, typically present but often asymptomatic until late in the course.[20] Cardiomyopathy is the cause of death in about 65% of people with Friedreich ataxia.[20]
- Skeletal symptoms
  - Kyphoscoliosis may be an early presenting feature with higher prevalence of double thoracic and lumbar curves in 60% to 79% of patients.[3,16,18–20]
  - Foot deformities in 52% to 74% of patients.[3,16,18–20]
- Endocrinologic symptoms
  - Excessive thirst and urination caused by glucose intolerance or frank diabetes mellitus in 8% to 32% of patients.[3,16,18]

EPIDEMIOLOGY

- Most common inherited ataxia, accounting for up to half of all genetic ataxias and as much as three-quarters of inherited ataxia in individuals younger than 25 years of age.[2,21]
- Prevalence rate is 1 in 30,000 to 50,000 people of white descent.[2]
- Approximately 1 in 100 people carry a mutant copy of *FXN*.[21]
- Most prevalent in the Americas, Europe, Australia, Asia, the Middle East, North Africa, and India because of a founder mutation in the white population with spread to these regions. It is least prevalent in China, Japan and Central Africa.[22]
- Onset typically in early teens, although may range from 2 years of age to the early 70s.[16]
- Disease duration: 75% survive longer than 34 years from onset of symptoms.[17]