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Clinical Features of Friedreich Ataxia

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Abstract

Friedreich ataxia, the most common hereditary ataxia, affects about 1:29 000 Caucasians. In about 98% of these individuals it is due to homozygosity for a GAA trinucleotide repeat expansion in intron 1 of *FXN*; in the other 2% it is due to compound heterozygosity for a GAA expansion and point mutation or deletion. The condition affects multiple sites in the central and peripheral nervous system as well as a number of other organ systems, resulting in multiple signs and symptoms. Onset of this autosomal recessive condition is usually in the first 2 decades of life. Major clinical features include progressive ataxia, absent lower limb reflexes, upgoing plantar responses, and peripheral sensory neuropathy. The main non-neurological sites of morbidity are the heart, resulting in cardiomyopathy, and the pancreas, resulting in diabetes mellitus. In this review, we provide an overview of the clinical features of Friedreich ataxia and discuss differential diagnoses.

Keywords

Friedreich ataxia; neuropathy; spinocerebellar; cerebellum; cardiomyopathy; diabetes mellitus

Nikolaus Friedreich first described Friedreich ataxia in a series of 5 papers published from 1863 to 1877.^{1–5} Friedreich recognized many of the main features of the disorder subsequently named after him, including an onset most often occurring in adolescence, ataxia, sensory neuropathy, scoliosis, foot deformity, and cardiomyopathy. During the next 100 years, precisely what comprises the clinical spectrum of Friedreich ataxia was the subject of some confusion and debate. With discovery of the causative gene in 1996,⁶ *FXN* (previously called *X25* and *FRDA*), rapid and accurate diagnosis of Friedreich ataxia can now be made in most instances. This has allowed studies to accurately assess clinical features of the condition. Almost all with Friedreich ataxia (~98%) have homozygous expansions of an intron 1 GAA trinucleotide repeat in *FXN* as the causative mutation; the other 2% are compound heterozygous for a GAA repeat expansion and a point mutation or deletion. The size of the smaller repeat correlates with the presence of a number of clinical features and negatively correlates with age at onset, but repeat size cannot be accurately used to predict prognosis in an individual.^{7–10}

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Friedreich ataxia most commonly affects individuals of Caucasian descent. It is very rare in those from Southeast Asia and Africa. It accounts for about half of all genetic ataxia and three quarters of inherited ataxia in people under 25 years.¹¹ On the basis of molecular studies, the estimated incidence of Friedreich ataxia in Caucasians is about 1 in 29 000, with a carrier frequency of 1 in 85.¹² Because the inheritance of Friedreich ataxia is autosomal recessive, it generally affects one or more members of a sibship but rarely affects more than one generation of a family.

The first attempt to define diagnostic criteria was by Geoffroy and colleagues (Table 1).¹³ Harding proposed less stringent criteria in 1981 (Table 2).¹⁴ With the discovery of the causative gene, these criteria have proved to be very specific but not particularly sensitive, with about 25% of affected individuals not fulfilling these criteria.

Friedreich Ataxia Due to Homozygous *FXN* Intron 1 GAA Expansions

Onset and Progression

Friedreich ataxia typically presents prior to 25 years, with the average age of symptom onset occurring in the early to mid-teen years.^{7,8} Atypical Friedreich ataxia refers to disease that does not meet classical criteria. There are 2 main atypical presentations: Friedreich ataxia with retained reflexes and late-onset Friedreich ataxia. Friedreich ataxia with retained reflexes often presents with brisk lower limb reflexes, particularly knee jerks, and is found in about 9% of affected individuals.¹⁵ Late-onset Friedreich ataxia, characterized by symptom onset after 25 years, is found in about 14%,^{8,16} while very late-onset Friedreich ataxia, characterized by onset after 40 years, is very rare.¹⁷

Friedreich ataxia is a relatively slowly progressive disorder. Average time from onset to requiring a wheelchair for mobility is about 10 years.^{7,8} Three studies have looked at mortality in Friedreich ataxia. Harding found the average age at death was 37 years,¹⁴ whereas De Michele and colleagues found that average time from onset to death was 36 years.¹⁸ A recent study involving 61 participants reported that the mean age at death was 37.5 years, while the median was 30 years.¹⁹ Causes of death were as follows: cardiac dysfunction (59%), probable cardiac dysfunction (3.3%), non-cardiac (27.9%), and unknown (9.8%).

Neurological and Neuromuscular Manifestations of Friedreich ataxia

Major clinical features of Friedreich ataxia and their frequency are shown in Table 3. Progressive trunk and limb ataxia, dysarthria, and muscle weakness are almost invariably present. Ataxia is by far the most common presenting symptom in Friedreich ataxia and is due to a combination of cerebellar and spinocerebellar degeneration, sensory neuropathy, and vestibular nerve involvement. Axonal neuropathy usually results in absent lower limb reflexes in the presence of upgoing plantar responses that are caused by degeneration of the corticospinal tracts in the spinal cord. A peripheral sensory neuropathy is common and reduced/absent vibration sense and proprioception result from degeneration of the posterior columns of the spinal cord. In addition, cold, cyanosed distal lower limbs due to autonomic disturbance may be seen, particularly in the latter stages of disease.¹¹

Scoliosis is present in most of those with Friedreich ataxia, with a high prevalence of double thoracic and lumbar curves.^{20–22} In one study, 20% of individuals with Friedreich ataxia required the prescription of a brace and 33% required spinal fusion.²¹ Pes cavus is common, occurring in 55% to 75% of individuals with Friedreich ataxia (Table 3), but it rarely causes morbidity. Equinovarus deformity of the feet is more commonly a cause of morbidity. In one study, equinovarus deformity that was of moderate severity but was reducible was diagnosed in 8 of 32 subjects, and severe non-reducible deformity was present in 9 of 32.²³

Vision can be affected by a number of pathological processes. In one large study,⁸ 13% of people with Friedreich ataxia were found to have visual loss, and 30% had optic atrophy¹⁴ Fortuna and colleagues found 26 of 26 individuals with Friedreich ataxia had anterior and posterior visual pathway abnormalities when assessed by optical coherence tomography and pattern visual evoked potentials, and all had reduced retinal nerve fiber layer thickness. Only 5 of 26 had visual symptoms, however.²⁴ Sudden loss of vision similar to that which occurs in Leber hereditary optic neuropathy is a well-described, albeit rare event in Friedreich ataxia. Abnormalities of eye movements are very common in Friedreich ataxia. The most commonly seen are square wave jerks; abnormalities of saccades, pursuit, fixation, and vestibular-ocular reflex are also commonly seen.²⁵ As a result of the impact of Friedreich ataxia on the visual system, visual quality of life is reduced in affected individuals.

Dysarthria is present in more than 90% of individuals affected by Friedreich ataxia (see Table 3). In a study of dysarthria in 38 individuals with the condition, 3 symptom subgroups were identified: (1) mild dysarthric symptoms, (2) increased velopharyngeal involvement, and (3) increased laryngeal dysfunction.²⁶ Severity of dysarthria was found to correlate with disease duration. Dysphagia is problematic for some individuals with Friedreich ataxia, particularly in the latter stages of disease; however, there are no systematic studies of this aspect of the condition. Aspiration pneumonia secondary to dysphagia is an important cause of morbidity and mortality.

Hearing loss is found in 8% to 13% of individuals with Friedreich ataxia (see Table 3). When hearing in conditions of background noise is assessed (which is a more realistic measure of real-life hearing than testing with no background noise), hearing problems are very common in Friedreich ataxia.^{27,28} Auditory neuropathy affects a significant minority. The use of FM-listening devices has been shown to improve hearing and communication.²⁹

Friedreich ataxia was traditionally thought not to affect cognition; however, more recent studies have shown that specific aspects of cognitive function are affected in many. Mantovan and colleagues found that the average IQ of people with Friedreich ataxia (92.8) was not significantly different than that noted in controls (110.8).³⁰ However, examination of the neurobehavioral profile of participants with Friedreich ataxia revealed impairment in verbal fluency, visuoconstructive and visuospatial capacity, and motor and mental reaction times. Mantovan and colleagues concluded that the intelligence profile of individuals with Friedreich ataxia is characterized by concrete thinking, poor capacity in concept formation, and visuospatial reasoning with reduced speed of information processing. More recent studies have also reported individuals with Friedreich ataxia are significantly disadvantaged in accommodating unexpected movement, initiating movement without a direct visual cue, and reacting to incongruent, compared with congruent, stimuli.^{31–34} Moreover, impairment in the cognitive control of ocular movement^{35,36} and difficulty with attention and working memory have also been demonstrated.³⁷

As with most neurodegenerative conditions, affective disorders are more commonly seen in those with Friedreich ataxia than in healthy controls. Flood and Perlman³⁸ found 35 of 38 individuals with Friedreich ataxia had an affective disorder, ranging from a grief reaction to major depression. In a small study, personality profiles outside the normal range — including poor impulse control, irritability, and blunting of affect — were noted.³⁰

Urological symptoms are common in Friedreich ataxia. In a cohort of people with Friedreich ataxia followed in Melbourne, 78 of 133 (59%) reported some problems with bladder function (unpublished data). These problems include hesitancy, urgency, retention, and incontinence. The requirement for an in-dwelling catheter is rare.

Other Major Clinical Features of FRDA

Cardiomyopathy is found in most people with Friedreich ataxia. This may result in symptoms of heart failure or palpitations but is often asymptomatic.³⁹ An abnormal electrocardiogram is found in almost all and in particular T wave inversion, left-axis deviation, and repolarization abnormalities are common.⁴⁰ Hypertrophic cardiomyopathy is seen on echocardiography in around 65% in cross-sectional studies (see Table 3), whereas almost all will have abnormalities when more subtle assessments such as Doppler ultrasound⁴¹ and magnetic resonance imaging are used.⁴² Septal and lateral long-axis dysfunction is common.⁴¹ Cardiac wall thickness often decreases as disease progresses⁴² and dilated cardiomyopathy may be seen, generally late in the disease course. Arrhythmias are common and can result in sudden death. Ejection fraction tends to remain normal until late in the disease course, with reduced ejection fraction being found in 20% of a large cohort.⁴³ Rarely, cardiomyopathy presents before ataxia develops.

Diabetes mellitus is present in 10% to 30% of people with Friedreich ataxia and impaired glucose tolerance is seen in a significant minority of others.^{7,8} Although impaired glucose metabolism in Friedreich ataxia is due to insulin resistance rather than insulin deficit, insulin therapy is usually required where diabetes mellitus occurs.

FRDA Due to Point Mutations and Deletions

As noted above, about 2% of Friedreich ataxia is due to compound heterozygosity for an intron 1 GAA expansion and a point mutation or deletion in *FXN*. The phenotype seen in individuals with some point mutations is indecipherable from that in those homozygous for *FXN*GAA expansions, but for others the phenotype differs.⁴⁴ p.Gly130Val is the most common point mutation and, compared with those with homozygous GAA expansions, individuals with this mutation generally have a later age of onset, slower disease progression, marked lower limb spasticity, and absent dysarthria and cardiomyopathy.⁴⁵

Differential Diagnosis

Friedreich ataxia is a condition with considerable variation in the extent of morbidity and mortality. Nevertheless, the clinical diagnosis of typical Friedreich ataxia is usually reasonably distinct, although early in the course there may be insufficient clinical features present to be certain. Atypical Friedreich ataxia and Friedreich ataxia due to compound heterozygosity for a *FXN*GAA expansion and a point mutation may present a greater diagnostic dilemma. Conditions that need to be considered in the differential diagnosis of FRDA include but are not limited to: (1) Ataxia — ataxia with vitamin E deficiency, ataxia with oculomotor apraxia types 1 and 2, ataxia telangiectasia, late-onset Tay-Sachs disease, ataxia due to mitochondrial DNA mutations; (2) Peripheral neuropathy — hereditary motor and sensory neuropathy, and (3) Spasticity — hereditary spastic paraparesis.⁴⁶

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Table 1Diagnostic Criteria Proposed by Geoffroy and Colleagues in 1976¹³

Primary (must be present)
<ul style="list-style-type: none">• onset before the end of puberty (never after 20 years)• progressive ataxia of gait• dysarthria• loss of joint position or vibration sense• absent tendon reflexes in the legs• muscle weakness
Secondary
<ul style="list-style-type: none">• extensor plantar responses• pes cavus• scoliosis• cardiomyopathy

Table 2**Diagnostic Criteria Proposed by Harding in 1981¹⁴**

Primary (must be present)

- onset before 25 years
- progressive ataxia of limbs and gait
- absence of knee and ankle jerks

Secondary

- dysarthria
 - extensor plantar responses
-

If secondary criteria are absent, the following have to be present: (1) an affected sib fulfilling primary and secondary criteria, (2) median motor nerve conduction velocities of greater than 40 m/s, thus excluding cases of type 1 hereditary motor and sensory neuropathy.

Table 3Major Clinical Features of FRDA and Their Frequency from 3 Studies⁴⁷

Symptom	Harding ¹⁴	Durr ⁸	Delatycki ⁷
Ataxia	99	100	100
Dysarthria	97	91	95
Absent lower limb reflexes	99	87	74
Scoliosis	79	60	78
Pes cavus	55	55	74
Swallowing disturbance	-	27	-
Sphincter disturbance	-	23	41
Reduced vision	18	13	-
Hearing impairment	8	13	-
Cardiomyopathy on echocardiogram	-	63	65
Diabetes/abnormal glucose tolerance	10	32	8