

Friedreich's ataxia

Abstract

Friedreich's ataxia (FA), an autosomal recessive neurodegenerative disease, is the greatest common of the inherited ataxias. The recent discovery of the gene that is mutated in this condition has led to rapid advances in Friedreich's ataxia understanding of the pathogenesis. Nearly 98% of the mutant alleles have an expansion of the GAA trinucleotide repeat in the intron of 1 of the gene. It leads to the reduced levels of the protein, and called frataxin. Friedreich ataxia is the result of the accumulation of iron in the mitochondria leading and to excess of the creation of free radicals, which formerly leads to the cellular damage and death. This chapter outlines genetics, the most conjoint clinical features of this disease: gait and limb ataxia, poor balance and coordination, sensory loss, leg weakness, impaired walking, areflexia, dysarthria, eye movement abnormalities, dysphagia, scoliosis, foot deformities, cardiomyopathy and diabetes. At present day there is no known treatment that changes the natural progression of this disease.

Keywords: autosomal recessive inherited disease, neurodegenerative disease, genetic mutation, frataxin, gait ataxia, areflexia, dysarthria, dysphagia, eye movement abnormalities, diabetes, cardiomyopathy, scoliosis, genetic counselling.

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Introduction

FA is an autosomal recessive inherited disease that causes progressive damage to the nervous system.¹ FA first was described by Nikolaus Friedreich, a German physician, in 1863.² Friedreich at first described the six patients in two families, with pathologically "degenerative atrophy of the spinal posterior columns", and clinically with poor balance, leg weakness, decreased walking, impaired coordination, dysarthria, nystagmus, impaired sensation, kyphoscoliosis and foot deformities.³ He also observed fatty degeneration of the heart in three cases. Critically, he identified the early age at onset, slow progression and inherited nature of the condition.⁴ All these features, together with early loss of deep tendon reflexes, form the core of the classical description of FA. The FA gene was open in 1996, leading to the better recognition of the spectrum of disease.⁴

Friedreich's ataxia is the most common form of hereditary ataxia, affecting about 1 in every 50,000 people in the United States. This is the most shared autosomal recessive ataxia, which accounts for just about 50 percent of all cases of hereditary ataxia. Although people from all parts of the world suffer from Friedreich's ataxia, and the studies show that their ancestry is almost always are European, North African, Middle Eastern or Indian (Indo-European). It is absent in populations in East Asia (China and Japan) and in American Indians.⁵

Most of the sick people with Friedreich ataxia begin to experience the signs and symptoms of the disorder between 5 and 15 years old. Poor coordination and balance often are the first noticeable of the features.⁶ Affected persons usually necessitate of the usage of a wheelchair nearly 10 years after signs and symptoms appear. Almost 25 % of the sick people with Friedreich ataxia have an atypical form in which signs and symptoms begin after 25 ages.³ Affected persons in which progress Friedreich ataxia between 26 and 39 ages are considered to have late-onset Friedreich ataxia (LOFA). When the signs and symptoms begin after 40 age the condition is called very late-onset Friedreich ataxia (VLOFA). LOFA and VLOFA usually progress more slowly than typical Friedreich ataxia.⁶

The classical clinical phenotype is the gait and limb ataxia with poor balance and coordination. Patients with progressive FA may have profound distal weakness of the legs and feet, that although significant about the weakness of the arms and it is rare before the patient becomes bedridden (Chawla 2016). Finally, the patient is unable to walk because of the progressive weakness and ataxia, becoming the wheelchair bound and an ultimately bedridden (2016).

Later dysarthria and dysphagia appears. Speech becomes slurred, slow, and eventually incomprehensible. Patients may experience mild weakening of the facial muscles with the associated weakness of swallowing. Incoordination of breathing, speaking, swallowing, and laughing can be the result of the patient nearly choking while speaking (Chawla 2016). The observed pattern of the neuropsychological impairment is an indicative of the executive problems and parietotemporal dysfunction. Thus, the cognitive impairment in FA is probably caused by the interruption of the cerebocerebellar circuits that have been proposed as the anatomical substrate of the cerebellar involvement in the cognition.⁸ The loss of the hearing and visual disturbance (the optic atrophy or nystagmus) are common. Bony deformities of the spine and feet (usually triggered by the neuromuscular problems) include the curvature of the spine (scoliosis), high-arched foot, clubfoot, deformities of the toes and foot inversion (foot turns inward). Onset is typically for around puberty with a slow progression and shortened life-span that often related to the cardiac complications.⁹ Early-onset cases are deteriorated the rapidly and are more frequently associated with the non-neurological features such as diabetes (in 10% of cases), cardiomyopathy (in 75% of cases), scoliosis and pes cavus. Late-onset cases have smaller GAA expansions and tend to have the slower progression.¹⁰

Genetics

The particular genetic mutation (expansion of an intronic GAA triplet repeat in the FXN gene (this nuclear gene encodes a the mitochondrial protein frataxin)¹¹ leads to the reduced expression of the frataxin.¹¹ Over the time this deficiency causes the aforementioned damage, as well as frequent fatigue due to the effects on the cellular

metabolism. The gene is located on the 9th chromosome. The mutant gene contains the expanded GAA triplet and repeats in the first intron;¹² in a few pedigrees, the point mutations have been detected. The defect is located in an intron (which is removed from the mRNA (Messenger RNA (mRNA) is a subtype of RNA. An mRNA molecule carries a portion of the DNA code to other parts of the cell for processing. mRNA is created during transcription. During the transcription process, a single strand of DNA is decoded by RNA polymerase, and mRNA is synthesized. Physically, mRNA is a strand of nucleotides known as ribonucleic acid, and is single-stranded) transcript between transcription and translation); this mutation does not result in the production of the abnormal frataxin proteins. In its place, the mutation causes the gene silencing (i.e., the mutation decreases the transcription of the gene) through the induction of the heterochromatin structure in a manner that similar to position-effect variegation.¹² Besides, the reducing expression of frataxin and long tracts of GAA are repeated induce chromosome breaks in in vivo yeast studies.^{11,12}

Frataxin is important for the normal function of the mitochondria and the energy-producing centers within cells. The research suggests that without a normal level of frataxin and certain cells in the body (especially peripheral nerve, spinal cord, brain and the heart muscle cells) cannot effectively to produce an energy and have been hypothesized to have a buildup of toxic byproducts leading because of what called "oxidative stress".¹³ One region of the FXN gene contains a segment of DNA that known as a GAA trinucleotide repeat. This segment is made up of a series of three deoxyribonucleic acid (DNA) building blocks (one guanine and two adenines) that appears the multiple times in the row. Normally, this segment is repeated from 5 to 33 times within the FXN gene. In people with Friedreich ataxia, the GAA segment is repeated from 66 to more than 1,000 times (Friedreich ataxia. Genetics Home Reference 2010). The length of the GAA trinucleotide repeats appears that to be related to the age at which the symptoms of Friedreich ataxia appear, how severe they are, and how quickly they progress. People with GAA segments repeated fewer than 300 times tend to have a later appearance of the symptoms (after 25 years) than those with larger GAA trinucleotide repeats.¹⁴ The abnormally long GAA trinucleotide repeats disrupts of the production of frataxin, which severely reduces the amount of this protein in cells. The certain nerve and muscle cells cannot function properly with the shortage of frataxin and lead to the characteristic signs and symptoms of Friedreich ataxia (Friedreich's Ataxia Fact Sheet 2014).

Pathology

Pathology related to FA includes the degeneration of the dorsal root ganglia and posterior columns of the spinal cord, spinocerebellar tracts, corticospinal tracts, dentate nuclei of the cerebellum and the heart.¹⁵ The major pathophysiologic finding in Friedreich ataxia is a "dying back phenomena" of axons, that beginning in the periphery with the ultimate loss of the neurons and the secondary gliosis. The primary sites of these changes are the spinal cord and spinal roots. This results in loss of large myelinated axons in peripheral nerves, which increases with an age and the disease duration.¹⁵ The unmyelinated fibers in sensory roots and the peripheral sensory nerves are spared. The posterior columns and corticospinal, ventral, and lateral spinocerebellar tracts all show the demyelination and the depletion of the large myelinated nerve fibers to the differing extents. This is accompanied by a fibrous gliosis that does not replace the bulk of the lost fibers.¹⁶ Overall, the spinal cord becomes thin and

the anteroposterior and transverse diameters of the thoracic cord are reduced. The dorsal spinal ganglia show the shrinkage and eventual disappearance of the neurons associated with the proliferation of the capsular cells.¹⁷ The posterior column degeneration accounts for the loss of the position and the vibration senses and the sensory ataxia. The loss of the large neurons in the sensory ganglia causes the extinction of the tendon reflexes.¹⁸

The large neurons of the dorsal root ganglia, especially lumbosacral, and nerve cells in the Clarke¹⁹ column, dentate nuclei, middle and the superior cerebellar peduncles are reduced in the number. Patchy are the loss of the Purkinje cells in the superior vermis of the cerebellum and of the neurons in corresponding portions of the inferior olivary nuclei are typical.²⁰ Mild degenerative changes occur in the pontine and medullary nuclei and optic tracts. The cerebellar ataxia is explained by the loss of the lateral and ventral spinocerebellar tracts and involvement of the Clarke column, dentate nucleus, superior vermis.¹⁹

The corticospinal tracts are relatively spared down to the level of the cervicomedullary junction. Beyond this point, the corticospinal tracts are severely degenerated, which becomes progressively more severe moving down the spinal cord. It explains the common finding of the bilateral extensor plantar responses and weakness late in the disease.²¹

Myocardial muscle fibers also show the degeneration and are replaced by the macrophages and fibroblasts. Essentially, chronic interstitial myocarditis occurs with hypertrophy of cardiac muscle fibers; fibers become hypertrophied and lose their striations.⁹ This is followed by the swelling and the vacuolation and finally the interstitial fibrosis. The nuclei appear hyperchromatic and occasionally vacuolated. The cytoplasm appears granular with frequent lipofuscin depositions.

Signs and symptoms

The onset of FA is early, with gait ataxia being is the usual presenting symptom. Typically, both lower extremities are affected equally. Some patients may have hemiataxia initially before the symptoms become generalized. In some instances, the ataxia begins abruptly following a febrile illness in which ataxia of one lower extremity precedes that of the other.

Gait ataxia manifests as progressively slow and clumsy walking, which often begins after normal walking has developed. The ataxia can be associated with difficulty standing and running. The gait ataxia is both of a sensory and the cerebellar type. This combination has been referred to as a tabetocerebellar gait. Opinions are conflicting as to whether the sensory or cerebellar features predominate. The cerebellar features of the gait ataxia in FA include a wide-based gait with the constant shifting of the position of the maintain balance. Sitting and standing are associated with the titubation.

The ataxia is the mixed origin, resulting in the spinocerebellar degeneration, peripheral sensory neuropathy, cerebellar and vestibular pathology.²² Pyramidal signs later add to the disability. The gait becomes unsteady and ataxic with increasing falls. Walking on the uneven terrain or in poor light becomes problematical. The difficulty with the tandem of standing and walking is an early sign. Many patients in retrospect describe a long history of clumsiness, trips or inability to participate in sports.³ There is increasing dependence

on aids to walking, initially furniture, walls and other people, and ultimately sticks, crutches and wheeled walkers. Truncal ataxia results in swaying on sitting and may necessitate back support. Romberg's test becomes positive or there may be difficulty early in the disease progression with the standing in tandem.³ Limb ataxia causes increasing difficulty with daily activities which require the fine manual dexterity and is an early feature of the disease. This causes difficulty with handwriting, washing, dressing, and use of the cutlery and carrying drinks or food. 99% of cases showed that the fingernose ataxia. In the lower limbs (LLs), 72% of cases had heel-shin ataxia, but all the remaining 28% could not be tested because of profound muscle weakness.²² Progression of weakness may, therefore, mask ataxia as a clinical sign.³

Pyramidal weakness is the relatively late sign and is much more prominent in the lower limbs compared to the upper limbs (ULs): indeed, patients often have very well preserved UL power even when wheelchair-bound and profoundly disabled, and may only ever develop mild distal UL weakness.³ However, this can contribute significantly to the difficulties with fine manual dexterity. Mild weakness is found of the ULs in 45% of cases and severe weakness in only 2%.³ By contrast in the LLs, 30% of cases have mild weakness and 28% of cases – severe weakness.³ Filla et al. noted 46% weakness of the ULs and 80% weakness in the LLs.²³ Wasting is noted in a significant proportion of cases although, in the patients in which develop the disease in early life, muscle bulk may never be fully developed without significant loss thereafter. Mild distal UL wasting is present in 39-49% of cases; LL distal wasting is present in 39-61% of cases.²⁴

Areflexia, particularly of the LLs, is an early sign present in almost of all patients and reflects the underlying peripheral neuropathy. Harding found all reflexes were absent in 74% of cases with the biceps reflexes present in 25% and the patellar reflexes in just 1%.²⁵ Delatycki et al.²⁶ found LL reflexes present in 2% of cases. Dürr et al.²⁶ found LL reflexes present in 12% of cases, reflecting the inclusion of the atypical cases in this series. Schöls et al.²⁷ found LL reflexes absent in all typical cases and present in 33% of atypical cases.²⁷ McCabe et al.²¹ found UL reflexes absent in 89% of the typical cases and 45% of atypical cases, whereas LL reflexes were absent in 100% of typical cases and 27% of atypical cases.²¹ The extensor plantar reactions, the reflecting pyramidal pathology, are a relatively early sign present in 73-89% of cases.²⁴⁻²⁶ Harding found flexor plantar reactions in only 1% of cases.²⁵ Again, extensor plantar reactions are less frequently seen in atypical cases.²⁷ Muscle tone is typically normal or reduced, particularly in the early stages of the disease. Harding found decreased UL tone in 24% of cases and increased UL tone in no cases.²⁵ The tone was decreased in the LLs in 16% of cases and increased in 12%. Spasticity, particularly in the lower limbs, can become a significant management problem in the advanced stages of the disease, especially in wheelchair bound patients.²⁵ It can cause pain, discomfort, positioning problems and ultimately contractures if left untreated. It can be associated with muscle cramps and spasms, which can often keep patients awake at night. The distal sensory loss is virtually universal in the classical phenotype, with the dorsal column modalities of vibrations and joint position sense preferentially lost, contributing to the sensory ataxia.³ Estimates of loss of vibrational sensibility vary from 73 to 88%,²⁴⁻²⁷ but pin prick sensation sometimes is also lost. Neurophysiological studies show a severe axonal neuropathy with severely reduced or absent sensory action potentials which do not appear to change significantly of over

the time. Peripheral nerve biopsy shows an increase in the proportion of the large myelinated fibres. Both of these findings correlate with GAA expansion size.¹⁸

Abnormalities of the eye movements are a common early sign in FA. Probably the commonest feature is fixation instability interrupted by involuntary saccades, or square wave jerks (SWJs), which can occur in the primary position, horizontal or vertical fixation. It is were found in all patients by Furman et al.²⁸ and Fahey et al.²⁹ and in 69% of cases by Schöls et al.²⁷ It is typically horizontal gaze-evoked nystagmus on the lateral gaze, and less commonly on the vertical gaze. Ptosis is found in a small but significant proportion of cases, possibly 5–10%.^{23,27} The decreased visual acuity is less commonly seen than eye movement abnormalities and the majority of the patients are asymptomatic. Approximately, 20% of patients have decreased visual acuity^{24,25,30} including occasional patients who have sudden bilateral loss of vision, mimicking Leber's hereditary optic atrophy. 30 % of patients have pallor of the optic disc visible on the fundoscopy.²⁵ For symptomatic patients, field loss may show generalized concentric field loss, concentric superior-inferior arcuate defects or isolated paracentral field loss.³⁰ Despite the lack of symptoms, all patients show reduced retinal nerve fibre layer thickness throughout all four quadrants on the optical coherence tomography. Pattern visual-evoked potentials show an increased latency in 34–70% of patients.^{24,30,31} These findings taken together suggest that the entirety of the visual system is involved in FA, although relatively few patients are clinically affected.

Dysarthria is a common and early sign present in more than 90% of individuals which progresses with disease duration.³ Speech becomes slow and slurred, impairing intelligibility in advanced cases. A study of 38 individuals with FA showed that 68% had mild dysarthria characterized by the consonant imprecision, decreased pitch variation, impaired loudness maintenance, reduced phrase length, hypernasality and impaired breath support for speech.³² Cluster analysis revealed two further subgroups with increased laryngeal dysfunction (13%) and increased velopharyngeal involvement (11%).³ Mild dysphagia is again a common symptom and can become problematical in advanced disease, occasionally requiring percutaneous endoscopic gastroesophageal tube insertion.³ Patients may cough or choke on solids or liquids including saliva.

Hearing difficulties because of an auditory neuropathy are a common and understated problem which can be very socially disabling even in the early stages of the disease. Reported prevalences of hearing the loss in case series vary widely from 8 to 39%^{24,25,27,33} with Harding²⁵ finding mild deafness in 5.2%, moderate in 1.7% and severe in 0.9%. Sound perception, as measured by the hearing thresholds across audiometric frequencies (250–8000 Hz) in a quiet room, is typically normal in FA³⁴ or there may be minor deficiencies at the different frequencies.^{35,36} However, almost of all patients shows disordered neural conduction in the central auditory pathways which functionally results in impaired speech understanding in conditions of the background noise typical of everyday listening conditions, which can lead patients to be able to access only 50% of the information that available compared to unaffected individuals.³⁷ Peripheral auditory (outer and middle ear) function is generally unaffected, as shown by the normal tympanometry and equal air and bone conduction in the pure tone audiometry.³⁶ Preneural cochlear responses, such as otoacoustic emissions, are also normal.³⁵ However, the retro cochlear and brainstem responses, such as acoustic reflexes, synthetic sentence

identification with an ipsilateral competing message and brainstem-evoked auditory potentials, are abnormal.^{38,35,36} In particular, there is appears that to be impairment of the temporal resolution of the complex acoustic signals as shown by the temporal discrepancies between otoacoustic emissions, cochlear microphonics and brainstem-evoked auditory potentials.³⁴ Such auditory neuropathy as dys-synchrony grossly impairs the ability to perceive rapidly changing auditory signals which are vital for phoneme discrimination and so speech perception. Recently, it has been shown that in FA patients with electrophysiological evidence of auditory neuropathy, binaural speech processing is impaired.³⁴ Although, "decrease in I.Q. (intelligence quotient)" was specifically mentioned in the first clinical criteria for FA,³³ most early studies concluded that cognition was not affected in FA other than slowed information processing.³⁹ The assessment of the cognitive function can be significantly hampered by motor, speech and auditory impairments influencing reaction times, fluency, and comprehension. Clinicians' general experience is that cognitive deficits do not impede participation in the education, employment or the social activities.³ More recently, Mantovan et al. showed the impairments in tasks related to the visuoconstructive and the visuo-perceptual capacity, the verbal fluency and the motor and mental reaction times.⁴⁰ The intelligence profile of FA patients were characterized by concrete thinking and poor capacity in concept formation and visuospatial reasoning. De Nobrega et al. found that patients with FA performed significantly worse in tests of the phonemic and action fluency but not semantic fluency when compared to controls.⁸ They are postulated that this might represent the primary prefrontal or cerebello-prefrontal dysfunction.

Corben et al.¹⁹ used a variety of tests to examine psychomotor functions of patients with FA. Patients had difficulty accommodating unexpected movements, that were disadvantaged by conditions requiring initiation of the movement without a direct visual cue, and were differentially affected in the reaction time to incongruent, compared with congruent stimuli.¹⁹

They are suggesting these deficits because of cerebellar impairment disrupting cerebro-ponto-cerebello-thalamo-cerebral loops. Kloppe et al.⁴¹ found the deficits in sustained volitional attention and working memory in FA.⁴¹ Neito et al.⁴² examined performance in the tasks measuring information that processing speed, attention, working memory, executive function, verbal and visual memory, language, visuo-perceptive, visuospatial and visuoconstructive functions in 36 patients with FA compared to controls.⁴² They found deficits in the motor and mental speed, conceptual thinking, verbal fluency, acquisition of the verbal information, use of the semantic strategies in retrieval, action naming, visuo-perceptive and visuoconstructive problems. They suggested these deficits indicated parieto-temporal dysfunction. Taken together, these studies provide evidence in the growing field of cerebellar cognitive function and suggest that interruptions of the cerebro-cerebellar circuits may be functionally important in FA.³

A variety of the other features have been reported in the presence of FA and although not necessarily related. These have included the tremor,^{33,25} epilepsy⁴³ and congenital malformations.⁴³ A recent study has looked at a possible association between the malignancy and FA and found that there was no association either at a molecular biological level or in the large population studies.⁴⁴ As with all chronic disorders, depression is more prevalent than in the unaffected population. Flood

and Perlman found that 92% of patients with FA showed an affective disorder ranging from mild mood disturbances to major depression (8%).⁴⁵ Epstein et al.⁴⁶ found that the Modified Fatigue Impact Scale was significantly worse in FA patients than controls.⁴⁶ Fatigue can be a significant problem in some patients which often limits attempts at the rehabilitation or ongoing exercises to maintain physical function. Autonomic changes have gained little attention in the literature. Filla et al.²³ found vasomotor disturbance or hyperhidrosis of the extremities in 48% of patients.²³ Hyposmia has been reported by Connelly et al. in FA patients.⁴⁷

Evidence of the cardiac complications is found if sought in probably the majority of cases of FA although the patients are very often asymptomatic. It is rare for cardiomyopathy to develop before neurological features, and even if the patient is initially referred to a cardiologist, on detailed history or examination, neurological features will be found which preceded the cardiac complications. The ischaemic heart disease is also rare.³ In a large of cases series, hypertrophic cardiomyopathy or evidence of left ventricular hypertrophy (LVH) was found in 28 to 100%^{48,23,26,24,33,21,27} although, the definitions vary widely between studies. Asymmetric septal hypertrophy or dilated cardiomyopathy are less commonly seen and may represent the progression from hypertrophic cardiomyopathy.⁴⁹ The blood pressure is typically normal or low, and hypertension is rarely a problem.⁵⁰

The absence of the correlation between the presence of cardiac complications and severity of neurological involvement has been reported⁵⁰ emphasizing the importance of the cardiac monitoring in all groups. The disjunction between cardiac and neurological feature may result from tissue specific somatic instability and mosaicism of the GAA triplate expansion. The electrocardiogram is abnormal in almost all of cases, the commonest anomaly being inferolateral or widespread T-wave inversion. Other non-specific ST segment and T-wave abnormalities, including ST-segment depression or elevation and flattening of T waves, are also seen.^{51,52} Electrocardiogram evidence of left ventricular hypertrophy (LVH) is seen less frequently and if present is usually accompanied by the echocardiographic evidence of LVH. QRS axis deviation is variable but most commonly to the right.⁵⁰⁻⁵³ Conduction abnormalities are very rare.^{50,52} Sinus rhythm or sinus tachycardia is usually found, although patients may be troubled with the paroxysmal or sustained arrhythmias, particularly atrial fibrillation, and only rarely require a pacemaker or defibrillator insertion.⁵⁴

The echocardiographic studies show again very variable results between patients. LVH is usually seen which is most commonly concentric but can show asymmetric septal hypertrophy.⁵¹ There is impaired systolic function but with relatively preserved ejection fraction. In a longitudinal study including 113 echocardiograms of children, median ejection fraction was 61%.⁵³ Systolic function shows a slow non-linear decline with an ejection fraction that decreasing more rapidly with increasing age.^{53,54} The cardiac valves are generally normal but the hypertrophied papillary muscle may be seen.⁵¹ In a large study of 204 patients with FA, 140 (69%) had evidence of cardiomyopathy, of which 58.5% were classified as mild, 23.5% intermediate and 18% severe.³ The mean interventricular septal thickness at diastole across these groups was 12.0 mm, whilst left ventricular posterior wall thickness at diastole was 10.8 mm and ejection fraction 63.2%.⁵⁰ A study of 173 patients showed evidence of diastolic dysfunction in 84% of cases with pseudonormalization

and impaired relaxation being the commonest descriptions.⁵⁴ Cardiac magnetic resonance imaging studies have broadly confirmed the echocardiographic studies^{55,50} with an increased left ventricular mass seen in FA, especially with a short disease duration and longer GAA size. It seems to be a tendency to left ventricular thinning with a longer disease duration.⁹

The association between FA and diabetes mellitus, although suspected for many years, was only confirmed relatively late.^{56,57} The mechanism of this is unclear but may relate to a combination of both insulin resistance of the peripheral tissues such as muscle, and also decreased insulin secretion resulting from the pancreatic beta cell dysfunction.⁵⁸ These abnormalities, in turn, are likely the result of the mitochondrial dysfunction. There does not appear to be an underlying immune pathology driving these changes.⁵⁹ There is some evidence that heterozygous carriers of the GAA expansion in the frataxin (FXN) gene may have increased incidence of an insulin resistance.^{60,11} In case of series, diabetes mellitus was found in 6–19% of cases^{43,23,26,24,33,21,27} found evidence of diabetes or impaired glucose tolerance in 32% of cases. Diabetes is typically a later feature of FA.²⁴ Patients sometimes require insulin treatment.

Scoliosis is common although may be mild and not require surgery especially if disease onset is relatively late. Labelle et al.⁶¹ found scoliosis of more than 10 degrees in 100% of patients and hyperkyphosis in 66%.⁶¹ The most cases showed the double thoracic and the lumbar curves.

Milbrandt et al. in the group of 77 patients found that 63% had scoliosis and 24.5% hyperkyphosis (Milbrandt, 2008). 33% of patients had a double major curve. 20% were treated with braces and 33% underwent a spinal fusion (Parkinson 2013). In other case of the group, from 33 to 94% of patients had scoliosis, most series finding a prevalence of more than 75%^{48,23,26,24,33,21,27} foot abnormalities are common. The case series shows a foot deformities in 55 to 90% of cases.^{48,23,26,24,33,21,27}

Friedreich observed that the both pes cavus and talipes equinovarus occur, either singly or in combination. Talipes equinovarus is more common in the classical cases. Sometimes pes planus is also seen.²⁵ Talipes equinovarus is a progressive condition was founded in an advanced disease and can be very disabling to mobility, transfers, and seating. If the patient is still ambulant, it can prevent proper placement of the foot on the floor and so contribute to instability and requirement for walking aids or orthotic devices. If the patient is wheelchair bound, it can impede the positioning and transfers (Delatycki et al., 2005). Therefore it can increase care demand and affect independence and quality of the life. Delatycki et al. studied the equinovarus deformities in 32 Australian individuals with FA and found absent or mild deformities in 15%, moderate but reducible (dynamic) deformities in 25% and severe and irreducible (static) deformities in 28% (Delatycki et al., 2005). The severity of deformity correlated with the current age, duration of disease and duration of the wheelchair dependence, but not GAA size or age at onset. Foot deformities, particularly equinovarus deformities are a common cause of the morbidity with significant impingement on quality of the life.³

Differential diagnosis and investigations

The differential diagnosis is wide because many diseases can cause early-onset, progressive ataxia with a chronic course. Clinical

history and investigations should look for a toxic, metabolic and immune diseases, paraneoplastic disorders, malformations, posterior fossa tumours, multiple sclerosis, and leukodystrophies.⁵

An important differential diagnoses are conditions presenting with early onset cerebellar ataxia and various combinations of neuropathy, spasticity or foot abnormalities. This includes ataxia with vitamin E deficiency, ataxia with coenzyme Q10 deficiency, ataxia with oculomotor apraxia types 1 and 2, ataxia telangiectasia, late-onset Tay-Sachs disease, cerebrotendinous xanthomatosis, Refsum's disease, A β –lipoproteinemia.^{5,26} Also we differentiate with Charcot-Marie-Tooth disease, hereditary motor and sensory neuropathy, hereditary spastic paraparesis, autosomal recessive spastic ataxia of Charlevoix-Saguenay, and ataxia because of mitochondrial mutations such as polymerase-c.^{5,26}

Friedreich's ataxia cannot be confidently excluded on clinical grounds. However, FA is very unlikely in the presence of an early prominent cerebellar atrophy, general learning disability, and preserved sensory nerve action potentials.⁵

We also should consider other causes of scoliosis or cardiomyopathy (if these are presenting symptoms). A diagnosis of FA requires a careful clinical examination, which includes a medical history and a thorough physical exam, in particular looking for balance difficulty, loss of proprioception, the absence of reflexes, and signs of the neurological problems. The genetic testing now provides a conclusive diagnosis. Other tests that may aid in the diagnosis or management of the disorder include: electromyogram, nerve conduction studies, electrocardiogram, echocardiogram, MRI or computed tomography scans, blood tests and urinalysis, brainstem auditory evoked responses and visual evoked potentials, genetic counselling and tests.^{62–82}

Treatment

As with the many degenerative diseases of the nervous system, there is currently no cure or effective treatment for FA. Treatment focuses on relieving symptoms, keeping the condition from getting worse and prolonging life.⁵

A multidisciplinary approach is needed. This should include a neurologist, a geneticist, a genetic counsellor, physiotherapists, speech and language therapists, occupational therapists and social workers. Antioxidant therapy (coenzyme Q(10) (400 mg/d) and vitamin E (2100 IU/d)) has, in theory, a role to play in treating FA. It has been proposed that reducing the load of free radicals will slow the progression of the disease. Most trials so far have focused on antioxidant therapy.¹⁶

Supportive treatment may also include:⁵

- Treatment of the cardiac failure and/or arrhythmias – using of the standard treatments.
- Orthopaedic surgery if there are troublesome symptoms from scoliosis, pes cavus or equinovarus deformity of feet.
- Foot deformities may also be helped by botulinum toxin or splints.
- Passive exercises and warming for the peripheral cyanosis and cold feet.

- Diabetes (if present) will usually require insulin.
- Sphincter dysfunction symptoms (eg, urgency) should be monitored. Urodynamic assessment and treatments such as oxybutinin may be helpful.
- Sexual dysfunction may require the symptomatic treatment.
- Counselling or antidepressants for the depression (selective serotonin reuptake inhibitors (SSRIs) are probably the most suitable antidepressant).
- Dysphagia may require dietary modification or (in later stages of the disease) gastrostomy.

Prognosis

The outlook depends on many factors, including the time when symptoms start (there is a poorer prognosis the earlier the symptoms begin), how bad the symptoms are and the quality of the medical care. Average life expectancy is 40–50 years, but disease severity and progression vary; some patients live into their seventies (Schulz 2009). Loss of an ability to walk typically occurs about 15 years after diagnosis (15.5 ± 7.4 years, range 3–44 (Schulz 2009)). Typically, people with FA are confined to a wheelchair within 15 to 20 years after their symptoms begin. Many eventually become incapacitated. The median age of the death is 35 years (37.5 ± 14.4 , range 21–69), while females have the better prognosis with a 20-year survival of 100% as compared to 63% in men (Schulz 2009). The most commonly reported causes of the death are cardiac failure and arrhythmias. Recorded causes of the death also include diabetic coma, bronchopneumonia, stroke and wheelchair accident.⁵

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Conflicts of interest

Authors declare that there are no conflicts of interest.

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