Clinical Management Guidelines for Friedreich Ataxia

Chapter 1. Overview of Friedreich ataxia

Contents

This chapter of the Clinical Management Guidelines for Friedreich Ataxia and the recommendations and best practice statements contained herein were endorsed by the authors and the Friedreich Ataxia Guidelines Panel in 2022.

Disclaimer

The Clinical Management Guidelines for Friedreich ataxia ('***Guidelines***') are protected by copyright owned by the authors who contributed to their development or said authors' assignees.

These Guidelines are systematically developed evidence statements incorporating data from a comprehensive literature review of the most recent studies available (up to the Guidelines submission date) and reviewed according to the Grading of Recommendations, Assessment Development and Evaluations (GRADE) framework © The Grade Working Group.

Guidelines users must seek out the most recent information that might supersede the diagnostic and treatment recommendations contained within these Guidelines and consider local variations in clinical settings, funding and resources that may impact on the implementation of the recommendations set out in these Guidelines.

The authors of these Guidelines disclaim all liability for the accuracy or completeness of the Guidelines, and disclaim all warranties, express or implied to their incorrect use.

Intended Use

These Guidelines are made available as general information only and do not constitute medical advice. These Guidelines are intended to assist qualified healthcare professionals make informed treatment decisions about the care of individuals with Friedreich ataxia. They are not intended as a sole source of guidance in managing issues related to Friedreich ataxia. Rather, they are designed to assist clinicians by providing an evidence-based framework for decision-making.

These Guidelines are not intended to replace clinical judgment and other approaches to diagnosing and managing problems associated with Friedreich ataxia which may be appropriate in specific circumstances. Ultimately, healthcare professionals must make their own treatment decisions on a case-by-case basis, after consultation with their patients, using their clinical judgment, knowledge and expertise.

Guidelines users must not edit or modify the Guidelines in any way – including removing any branding, acknowledgement, authorship or copyright notice.

Funding

The authors of this document gratefully acknowledge the support of the Friedreich Ataxia Research Alliance (**FARA)**. The views and opinions expressed in the Guidelines are solely those of the authors and do not necessarily reflect the official policy or position of FARA.

1. Overview of Friedreich ataxia

1.1 Clinical features of Friedreich ataxia

Antoine Duquette and Ludger Schöls

1.1.1 Symptom onset and presenting symptoms

The disease which came to be known as Friedreich ataxia (FRDA) (1) was first described by the German pathologist Nikolaus Friedreich in a series of five papers published between 1863 and 1877 (2-6). At the time, Friedreich described a new hereditary spinal disease associated with kyphoscoliosis and fatty degeneration of the heart. The disease is most often caused by a pathogenic expansion in the first intron of the frataxin gene (7) and the size of the expansion influences the clinical presentation. Typically, the disease begins in early adolescence with gait instability (8). Scoliosis may also be the initial symptom, especially in patients with a younger age of onset (8).

1.1.2 Diagnostic criteria

The first set of diagnostic criteria for FRDA were proposed by Geoffroy and colleagues in 1976 (9). Seven primary signs and symptoms were considered obligatory for diagnosis: onset before the end of puberty and never after the age of 20; ataxia of gait; progression of ataxia within the last two years; dysarthria; decrease of joint position and/or vibration sense in lower limbs; muscle weakness; and deep tendon areflexia in the lower limbs. Four clinical features were considered secondary, but not obligatory for diagnosis: extensor plantar response; pes cavus; scoliosis; and cardiomyopathy. These criteria, however, proved to be difficult to use in younger individuals in whom some of the features deemed to be obligatory, such as muscle weakness and sensory loss, would develop later. To overcome this challenge, Anita Harding proposed a new set of criteria (10). Obligatory criteria included an onset of symptoms before the age of 25, progressive unremitting ataxia of the limbs and gait, as well as absence of the knee and ankle jerks. Dysarthria and extensor plantar responses were considered important secondary criteria.

While diagnostic criteria have been critical to guide research and clinical care, they restricted the expected presentation of individuals with FRDA. The identification of the genetic basis of the disease (7) has led to a significant expansion of clinical phenotypes associated with FRDA. The limitations of the criteria rapidly became apparent as genetically confirmed individuals had onset after the age of 25 or with retained tendon reflexes (11, 12). In fact, the phenotype of late-onset FRDA is often predominantly spasticity with very little ataxia (13).

1.1.3 Incidence and progression of clinical features

Neurological signs and symptoms

In longitudinal studies, the neurological symptoms progress over time. Loss of ambulation obviously has a significant impact on independence and quality of life. For individuals with disease onset before the age of 15, loss of ambulation occurs on average 11.5 years after disease onset with the sequential loss of stance with feet apart and eyes closed, followed by stance with feet together and, finally, normal stance (14). Dysarthria is a nearly universal feature in FRDA (11, 12, 15) and spectral measures can detect changes in speech over time (16). The prevalence and frequency of ocular square-wave jerks increases over time, but this rarely translates into functional impairment (17). Overall, using the Friedreich Ataxia Rating Scale (FARS), the disease seems to progress faster in

younger individuals (18). While disease progression may indeed slow down with time, this could also reflect the limitations of clinical scales currently in use.

Neurogenic bladder

Lower urinary tract symptoms, including hesitancy, retention, urgency, and incontinence, have been reported in 59% to 82% of individuals with FRDA (19, 20).

Orthopedic involvement

In cohorts with genetically confirmed FRDA, between 60% and 84% have scoliosis (11, 12, 15, 21). Pes cavus, which is slightly less frequent, is also observed in a majority of individuals with FRDA (11, 12, 15, 21).

Cardiac involvement and diabetes mellitus

Heart involvement in FRDA has been described by Nikolaus Friedreich in his original series of publications and cardiac disease is recognized as the most common cause of mortality in FRDA (22). In fact, in addition to GAA repeat length, left ventricular mass index and left ventricular ejection fraction are independent predictors of mortality (23). ECG abnormalities such as T-wave inversions are found in 83% of individuals with FRDA (12). While 78.6% of people with FRDA exhibit normal left ventricular function, ejection fraction declines slowly over time even if it remains within the normal range (23).

Diabetes mellitus is another significant issue associated with FRDA and often requires insulin therapy; prevalence has been estimated to be between 8% and 32% (11, 12, 15).

Visual impairment and hearing loss

While clinically significant visual loss is reported in a minority of people with FRDA, anterior and posterior visual pathway involvement is nearly universal (24). Hearing loss is also increased in FRDA relative to the general population, and abnormal speech perception has been described in up to 90% of people with FRDA (25).

1.2 Genetics and pathophysiology of Friedreich ataxia

Sanjay I. Bidichandani, Hélène Puccio and Robert B. Wilson

1.2.1 Genetics, incidence and carrier frequency

FRDA is caused by loss-of-function variants in the *FXN* gene (7). As an autosomal recessive condition, individuals with FRDA inherit disease-causing variants from both parents, each of whom is an asymptomatic carrier. By far, the most prevalent disease-causing variant in FRDA is an expanded GAA triplet-repeat sequence in intron 1 of the *FXN* gene. Indeed, about 96% of individuals with FRDA are homozygous for this mutation, which ranges in size from 100 to 1500 GAA triplets. Whereas rare alleles may fall outside of these bounds, the most common allele sizes encountered in practice range from 600 to 1200 triplets. Normal, non-FRDA alleles contain less than 36 GAA triplets, the majority of which are 8 to 12 triplets in length. The remaining 4% of individuals with FRDA are compound heterozygous with an expanded GAA triplet-repeat sequence in one of the *FXN* alleles, and another deleterious mutation in the other allele (26). The latter class of disease-causing variants include a variety of inactivating *FXN* mutations. These mutations, which are individually rare, include missense, nonsense, splice, and small insertion/deletion variants that span the entire length of the gene. Rare instances of large deletions have also been seen that involve an entire exon or multiple contiguous exons.

All individuals with FRDA genotyped to date have at least one expanded GAA triplet-repeat. Strong linkage disequilibrium indicates that the expanded GAA triplet-repeat arose from a relatively recent common founder (27). As a result, the expanded GAA triplet-repeat is seen predominantly in the Indo-European population, and in populations with whom they have admixed. The carrier frequency in Indo-Europeans is estimated to be about 1%, which supports an incidence rate of about 1 in 40,000.

1.2.2 Pathophysiology

The *FXN* gene encodes a mitochondrial protein called frataxin (28). The expanded GAA triplet-repeat results in *FXN* transcriptional deficiency, which is inversely correlated with the length of the repeat (29). Most individuals with FRDA are homozygous for expanded alleles containing more than 500 triplets, and typically express 5% to 10% frataxin transcript compared to non-FRDA levels. However, a subset (about 20%) of individuals have at least one expanded allele containing less than 500 triplets, which leads to a higher (10% to 20%) residual frataxin transcript level (30). Heterozygous carriers, such as parents of affected individuals, remain asymptomatic despite expressing about 50% of normal, non-FRDA levels of *FXN* transcript. Expanded GAA repeats cause *FXN* transcriptional deficiency via epigenetic silencing, and/or by the formation of an abnormal RNA-DNA hybrid structure called an R-loop, both of which are bona fide therapeutic targets in FRDA (31, 32).

Frataxin functions in the biogenesis of iron-sulfur (Fe-S) clusters (33), which are essential cofactors that participate in a number of cellular pathways including mitochondrial respiration, iron metabolism and DNA metabolism. In FRDA, deficiency of frataxin results in decreased mitochondrial ATP production, perturbed iron metabolism and dysregulated oxidative stress response (34). Tissues that are pathologically involved in FRDA tend to be highly dependent on mitochondrial oxidative phosphorylation (34-36). These include the nervous system (large sensory neurons of the dorsal root ganglia; spinocerebellar and corticospinal tracts as well as the posterior columns of the spinal cord; cerebellar dentate nuclei), the heart, and pancreatic β-cells. Tissue vulnerability and pathological involvement likely begin during embryonic development (37, 38) and continue throughout life to the later stages of disease; however, the precise pathophysiological determinants of disease progression in FRDA are not well understood.

1.3 Genotype phenotype correlations in Friedreich ataxia

Ariane Veilleux Carpentier and Antoine Duquette

1.3.1 Phenotype for individuals homozygous for GAA triplet repeat expansion

In individuals with FRDA who are homozygous for a GAA triplet repeat expansion, the smaller allele size (GAA1) partially predicts disease evolution, phenotype, and prognosis, while the larger allele (GAA2) expansion is a weaker predictor of clinical variation (79).

Age at onset

Age at onset of symptom depends on the size of the expansions of both alleles but mainly correlates with the length of GAA1 (8, 11, 15, 53, 79, 80). Both GAA1 size and age at onset influence the rate of disease progression, the duration from onset to wheelchair dependency, and the age of loss of ambulation (11, 53, 79). Individuals with late-onset FRDA or very-late-onset FRDA have smaller GAA1 expansions than typical FRDA and a milder disease progression (73). Notably, smaller GAA1 expansion size may be associated with adult-onset spastic ataxia (81) or with spasticity and little

ataxia (13). While GAA1 triplet expansions can account for 40% of the variability in age at onset and age at wheelchair dependency, GAA2 size is possibly responsible for 10% (53, 79).

No correlation has been found between GAA1 repeat length and age at onset of symptoms for individuals with non-neurological symptoms at onset (isolated cardiomyopathy or scoliosis) (51). The somatic instability of GAA repeats differs between tissues and may explain the lack of correlation between some symptoms, such as non-neurological symptoms, and GAA1 length (82).

Clinical features

Some clinical features of FRDA, such as dysarthria, sphincter disturbance, hearing loss, and decreased visual acuity appear to be linked mostly to disease duration (11, 79). GAA1 size correlates with the severity of proprioceptive impairment (23, 83-85) and pes cavus, scoliosis, and areflexia are more frequent with longer GAA1 expansions (11, 79). Both GAA1 and GAA2 repeat lengths correlate with dysphagia and lower-limb weakness (79).

Cardiomyopathy is the most frequent cause of mortality in FRDA. The increase in heart disease prevalence in association with higher repeat lengths became obvious when the first genotype-phenotype correlations were established (11, 53, 86). Evidence also suggests that left ventricular hypertrophy is significantly more prevalent in individuals with a GAA1 repeat size above 770 (84). More recently, another study showed that those with the worst cardiac evolution carry longer GAA repeats (23).

Diabetes mellitus is another important systemic non-neurological manifestation of FRDA, but the evidence regarding a correlation with repeat length is conflicting (11, 15, 53). Intriguingly, aberrant glucose metabolism has been shown to be associated with longer GAA1 repeat length (87).

1.3.2 Compound heterozygous phenotype

The phenotype of compound heterozygous individuals depends on the type of mutation on the non-expanded allele. Several mutations result in absent frataxin or loss of function and are associated with a typical FRDA phenotype (88). Individuals with missense mutations p.G130V and p.D122Y have an atypical phenotype with retained reflexes and without dysarthria (88). Null mutations result in an earlier age of onset and an increased risk of developing diabetes mellitus when compared to homozygous expansions (26). However, compound heterozygotes have a lower prevalence of cardiomyopathy (26).

See Chapter 12 for more details on compound heterozygosity.

1.4 Neuromorphology of the nervous system in Friedreich ataxia

Kathrin Reetz, Arnulf H. Koeppen and Marcondes C. França

FRDA is a slowly progressive multisystem disease with a complex pathogenesis. The proprioceptive system is affected early in the FRDA disease process, as well as the cerebellar, corticospinal, visual, auditory and autonomic systems and non-neuronal cell types, resulting in a unique clinical picture. For clinicians, effects on the nervous system and the heart are most relevant. However, understanding the multi-system complexity of FRDA and its temporal evolution is highly relevant for developing new therapies and defining targets (36).

1.4.1 Pathology

FRDA affects several sites in the central and peripheral nervous systems: the spinal cord, dorsal root ganglia, sensory peripheral nerves, the dorsal nuclei, gracile and cuneate nuclei in the medulla oblongata, and the dentate nucleus of the cerebellum. Medical students and other trainees will learn about spinal cord atrophy in FRDA, and indeed, stains of sections of the thoracic spinal cord reveal subtotal lag of myelinated fibers in the dorsal columns and a more moderate deficit of fibers in the lateral corticospinal and dorsal spinocerebellar tracts (see Table 1.1). However, while the histopathological diagnosis of FRDA can be made by inspection of spinal cord sections, the clinically more important lesion is located in the dentate nucleus, which shows loss of large neurons while small neurons are commonly preserved. By immunohistochemistry, the small neurons of the dentate nucleus contain glutamate decarboxylase, the enzyme that generates γ-aminobutyric acid (GABA), which is the most abundant inhibitory neurohumoral transmitter in the central nervous system (CNS). The GABA-ergic small neurons send axons to the contralateral inferior olivary nuclei that remain intact in FRDA. The vulnerable large dentate nucleus nerve cells are thought to be glutamatergic, hence are excitatory at the location of their synaptic terminals in the contralateral thalamus.

In most cases of FRDA, the cerebellar cortex remains intact, although in long-standing cases there is regional loss of Purkinje cells and atypical location in the molecular layer of the cerebellar cortex. A highly characteristic abnormality of the dentate nucleus in FRDA is “grumose” reaction – formerly considered a degeneration. It consists of clusters of GABA-ergic Purkinje cell-derived axon terminals about dendrites and cell bodies of large and small dentate nucleus neurons. The precise pathogenesis of grumose regeneration is unclear, but may be related to the deficient position of GABA receptors in the plasma membranes of dentate nucleus neurons. Trigeminal ganglia and the dorsal root ganglia at the spinal level are important targets in FRDA. Dorsal root ganglia display reduced sizes of all neurons, a remarkable proliferation of satellite cells, infiltration by monocytes, and neuronophagia of dorsal root ganglia neurons. A characteristic lesion is the formation of residual nodules that consist of a mixture of proliferated satellite cells and monocytes. Monocytes express markers of macrophages, such as CD68 and IBA-1 though phagocytosis is absent. The destruction of neurons is more akin to neuronophagia than to phagocytosis. Systematic quantification of the size of dorsal root ganglia neurons has led to the conclusion that the dorsal root ganglia lesion in FRDA is hypoplasia rather than atrophy. During development, intact dorsal root ganglia neurons are responsible for the proper growth of axons in the dorsal columns of the spinal cord and the trophic support of the dorsal nuclei that give rise to the dorsal spinocerebellar tracts. Accordingly, the time-honored “atrophy” of the spinal cord is also more consistent with hypoplasia than with degeneration. A critical point in the pathogenesis of the lesions in dorsal root ganglia and the spinal cord is failure of the boundary cap, a barrier at the junction of spinal cord CNS and the growing axons seeking entry into the parenchyma of the spinal cord. A remarkable observation at the level of the dorsal root entry zone is the invasion of dorsal roots by cones of glial tissue arising from the spinal CNS. Hypoplasia and inflammatory destruction of dorsal root ganglia neurons are also responsible for the neuropathy of sensory peripheral nerves, resulting clinically in reduced sensory function. The paucity and small size of nerve cells in the gracile and cuneate nuclei may be attributed to transneuronal atrophy.

1.4.2 Imaging

Clinically relevant imaging features supporting diagnosis

Typical FRDA radiographic structural features of the brain and spinal cord are: (i) thinning of the cervical cord (reduction in anteroposterior diameter), depending on the stage of the disease; (ii) mild cerebral atrophy; and (iii) mild to moderate cerebellar atrophy. Usually the atrophy is not as severe as in other spinocerebellar ataxias. Using diffusion weighted imaging, microstructural involvement of the structures, in particular the cerebral peduncles can be detected. Magnetic resonance imaging (MRI) of the brain and spinal cord can support the diagnosis of FRDA.

What do we know from multi-modal imaging in a research setting?

From the imaging point of view, there is a clear spino-cerebellar dominance with respect to the CNS. For the cerebellum, a pattern of gray matter atrophy weighted toward lobules IV–VI of the vermis, and reductions in brainstem and cerebellar white matter volume adjacent to the dentate nuclei and within the cerebellar peduncles, is well described (39-44). Atrophy of the dentate nuclei has also been reported using quantitative susceptibility mapping (QSM), alongside cross-sectional increases in iron concentration and longitudinal iron accumulation in these structures (45). Recently the spinal cord has gained increased attention. MRI evaluations of spinal cord morphometry have identified flattening and reduced cross-sectional area across the full length of the spinal cord, but most marked in cervical regions (39, 42). There are suggestions that spinal cord changes occur early in the disease, are progressive, and are clinically relevant features of FRDA, but this is still being debated.

For the cerebrum, reports of subtle anatomical changes remain mixed, with atrophy of the thalamus and cortical motor areas most consistently implicated and thought to reflect later-stage disease changes (39, 42). Robust microstructural white matter abnormalities have also been detected, most notably in corticospinal, callosal, and long-range association tracts (42-44, 46). Microstructural impairments appear to manifest over-and-above volumetric atrophy (40, 43) and correlate with biochemical markers of neuronal loss (N-acetyl-aspartate-to-creatine ratio) (46, 47). The patterns of abnormalities reported across different neuroimaging indices point to the potential for both myelin-related and degeneration-related white-matter disease in FRDA. Whole brain functional MRI (fMRI) studies in FRDA also reveal evidence of network-level functional changes. Reduced cerebro-cerebellar and increased cerebro-cerebral connectivity have been found using resting-state fMRI (40, 48). These studies indicate a potential for adaptive mechanisms to play a role in disease mitigation or expression.

Table 1.1 Overview of major neuropathological and imaging findings in Friedreich ataxia

Region	Pathology	Imaging
Cerebrum	Generally normal	*Morphometry:* atrophy of the thalamus and cortical motor areas (later stages) *Function/Connectivity:* ↓ cerebro-cerebellar and ↑cerebro-cerebral connectivity; cerebral compensation
Cerebellum	Atrophy of the dentate nuclei and their efferent fibers in the superior cerebellar peduncle. Loss of GABAergic and	*Morphometry:* atrophy weighted toward lobules IV–VI; atrophy of the dentate nuclei using QSM *Function:* ↓ cerebro-cerebellar connectivity

Region	Pathology	Imaging
	glutamatergic afferents in the dentate nuclei.	*Neurochemistry: (*vermis and/or cerebellar hemispheres): ↓tNAA (/tCr); tCr; mI
Brainstem	Gracile and cuneate nuclei	*Morphometry:* atrophy in the medulla oblongata, pons and mesencephalon
Cervical spinal cord	Dorsal column hypoplasia; underdeveloped dorsal roots	*Morphometry:* reduced cross-sectional area and volume, flattening *Neurochemistry*: ↓tNAA
Thoracic spinal cord	Lack of myelinated fibers in the dorsal columns, the dorsal spinocerebellar tracts, and the lateral corticospinal tracts. Hypoplasia of the dorsal nuclei	*Morphometry:* reduced cross-sectional area and volume, flattening

Legend: tCr, total creatine; tNAA, total N-acetylaspartate; mI, myo-Inositol; ↓reduced compared with controls; ↑ increased compared with controls. The listed findings are primarily based on review articles and meta-analyses; therefore, metabolite ratios are mostly displayed for MRS findings, and the respective metabolic reference is indicated in brackets, that is, (/tCr). The respective 'numerator' simultaneously represents the metabolite concentration from individual findings, that is, tNAA in tNAA (/tCr); QSM, quantitative susceptibility mapping

1.5 Early diagnosis of Friedreich ataxia

Sub H. Subramony and Katherine Mathews

1.5.1 Background

There is concern that there is excessive delay in confirmation of the diagnosis of FRDA after symptom onset. This will be important as definitive therapies for FRDA become available, since earlier initiation of treatment may produce better results. The path to diagnosis for these patients likely varies by geography and by presenting signs or symptoms. In the case of the typical patient with childhood onset, often the journey begins with complaints about motor difficulties addressed to the primary pediatrician and then referral to other specialists, either neurologists or orthopedic surgeons. Alternatively, many individuals with FRDA are found to have scoliosis before onset of neurological symptoms and are referred to orthopedics. Thus, pediatricians, orthopedic surgeons and pediatric neurologists need to be familiar with FRDA as a possible diagnosis in children who have motor difficulties or spinal deformities.

Experience in Europe has detailed the problems with early diagnosis of rare diseases in general (49, 50). The EFACTS consortium assessed the time to diagnosis in their cohort of 619 FRDA individuals, with 3.3% being compound heterozygotes (51). The median time to diagnosis was 3 years with an inter-quartile range of 1-7 years. Cases diagnosed before 1996 (when gene testing became available) had a median delay of 4 years and this was reduced to a median of 2 years in those seen after 1996. Those with non-neurological onset had greater delay in diagnosis than those with neurological onset (median of 5 years compared to 3 years). Similarly, a FARA (Friedreich Ataxia Research Alliance) survey primarily among US patients (poster presented at the IARC meeting 2018, n=2579) found the mean time between symptom onset and diagnosis ranged from 2.4 years in children diagnosed

below age 10 years; 3.9 years for patients aged 10 to 19 years; and 8.1 years for those aged 20 or above. The patients had often seen several health care providers before the correct diagnosis was made, with the common misdiagnoses being Charcot-Marie-Tooth disease (CMT), cerebral palsy, multiple sclerosis, "cerebellar abnormality" and inner ear disease.

1.5.2 Clinical picture

Prior to the availability of genetic testing, clinical diagnostic criteria for FRDA were developed by investigators from Canada and the UK (9, 10). Initial criteria had high positive predictive value (>90%) but low sensitivity (63%) (12). A more liberal set of criteria improved the sensitivity to 77% (52) (see Table 1.2).

It should be noted that despite a genetic etiology, most FRDA patients will not have a family history of FRDA because of the autosomal recessive inheritance pattern. With large sibships or in inbred populations, it is more likely the family history will include another affected family member.

Table 1.2 Diagnostic criteria for Friedreich ataxia

Geoffroy *et al.* (9)	**Harding** (10)	**Filla *et al.*** (52)
Onset < 20 years	Onset < 25 years	Onset < 20 years
Progressive ataxia	Progressive ataxia	Progressive ataxia
Lower limb areflexia	Lower limb areflexia	Lower limb areflexia
Decreased vibration sense	Dysarthria after 5 years	One of the following: Dysarthria, Babinski, LVH
Weakness	Small/absent sensory nerve action potentials (SAPs)	
Dysarthria		

Neurological onset

Symptoms

The majority of people with FRDA present with a neurological complaint; this was found in 90.7% of the large European cohort (51).

The mean age at onset for typical FRDA has been reported to range from 10.5 ± 7.4 years to 15.5 ± 8.0 years (9-11, 53, 54). In Harding's study, 40% had onset before 10 years of age and 10% before 5 years and onset can occur as early as 2 years of age (10, 54). Some authors note a bimodal peak for age at onset, one just below 10 and then 12 to 15 (54, 55) but Harding observed a single peak at 10-12 years (10). Late onset (onset after 25 years) has been observed in 6% to 14% of genetically diagnosed FRDA and in 17% of the large EFACTS cohort (11, 12, 15, 51). Exact age at onset may be difficult to determine because parents may report that the child was always "clumsy" and earliest signs and symptoms can be non-specific.

A progressive gait unsteadiness is the usual complaint at the onset in over 84% of cases (10, 11, 15, 54). Motor milestones are not delayed. Complaints can range from gait unsteadiness to "clumsiness" and tripping, falls, and poor hand function (9, 10). Other features that can bring the child to attention include a decline in athletic performance and an inability to keep up with peers in motor skills such as

bike riding. Dysarthria, tremor and vertigo and "asthenia" are the initial complaints in some individuals (51, 54). An unsteady stance and fidgety body movements to stand in place can result in a misdiagnosis of chorea (55-58).

Progression of symptoms is slow and may be missed over short periods of time. Harding criteria suggest progression over 2 years that is unremitting (10).

Signs

The discussion below is based on some of the larger FRDA clinical series and personal observations of the authors. It should be noted that the prevalence of various signs may not reflect early disease because the publications referred to patients assessed in various stages of the disease, with a mean duration ranging from 3.7 to 22 years.

Cerebellar signs and ataxia

Children with FRDA appear to lose the ability to stand on one foot, or tandem stance or stand with feet together with eyes closed very early in the process (59). Thus, in studies of the natural history of FRDA, these abilities were lost in almost all patients by the time they were seen at their initial visits. Gait becomes somewhat broad based and clumsy and there is an associated decline in the ability to run and jump. Many children appear to be fidgety (the term "static ataxia" was used by Friedreich for this sign and it may have a resemblance to chorea). In large clinical series gait ataxia was universal, characterized by a broadening inter-foot distance observed during stance and gait; lower limb ataxia is also nearly universal and is detected by the heel to shin slide revealing a side to slide oscillation of the heel on the shin bone.

Truncal and upper limb ataxia, as detected using the finger to nose test, rapid alternating movements and finger chase test, develop later in the disease.

Other clinical signs that indicate cerebellar disease include abnormal eye movements and dysarthria. Dysarthria may not become universal until after 10 years from onset (10) and was evident in only 60% by 5 years after onset. Nystagmus, the best-known feature of cerebellar dysfunction, may occur only in a minority of FRDA patients (10, 11, 52, 54, 55), but jerky pursuit, dysmetric saccades and fixation instability are more common. In studies done prior to molecular testing, a pattern of increased fixation instability, inaccurate saccades and impaired smooth pursuit with normal saccade velocity were reported (60-62). Fixation instability is characterized by easily visible, to and fro oscillations of the eyes during attempted fixation on a stationary object (square wave jerks).

Peripheral nerve signs and "neuropathy"

At an early stage in the disease, there is evidence for peripheral sensory nerve dysfunction (primarily proprioception) that contributes to the gait ataxia. Lower limb areflexia (often with areflexia in the arms as well) occurs within 5 years of onset in over 85% of cases (10, 11, 15, 52, 54). Sense of vibration is impaired in 69% to 93% of cases (10, 11, 15, 52, 54). Position sense can be lost even when vibration sense is preserved, but is not universal even 10 years after onset.

Muscle weakness

Muscle weakness occurs relatively late in FRDA (10, 11, 15, 54, 63). Harding (10) noted "pyramidal" weakness almost universally 10 to 15 years after onset, but in a substantial number even before that. The weakness is diffuse and different in pattern from that seen in muscular dystrophies. It is accompanied by ataxic difficulties in the leg and does not give rise to classical signs of weakness seen in muscular dystrophies, such as the Gowers maneuver.

Preserved neurological function

Cognition is preserved and there is no learning disability.

Non-neurological onset

Fewer than 10% of patients with FRDA have a non-neurological symptom at onset (10, 51, 63). Scoliosis is the most common non-neurological presentation followed by cardiomyopathy. Even when patients seek attention primarily for neurological symptoms, many may have a history of scoliosis detected by past screening examinations. Given that up to 5% of children have idiopathic scoliosis (64), the question of when a pediatrician or orthopedic surgeon should look more closely for a neuromuscular disorder is difficult to answer (65, 66). Some elements of a neurological examination (Table 1.3) should be included in the evaluation of children with scoliosis and any progression of motor disability should prompt neurological consultations. Also, FRDA gene tests should be strongly considered with early onset cardiomyopathy, despite two recent reviews of hypertrophic cardiomyopathy making no mention of FRDA (67, 68). Given that the FRDA repeat expansion cannot be detected by genetic sequencing, it should be kept in mind in children with suspected genetic cardiomyopathy.

Table 1.3 Early diagnosis of Friedreich ataxia: helpful clinical and laboratory features

- Normal early motor milestones
- Progressive imbalance in late first decade or early second decade for typical FRDA. Important to elicit history of increasing “clumsiness”, loss of athletic abilities, increasing difficulties with running, jumping, cycling (re-examine patients and listen to them and parents carefully for worsening motor function)
- Stance and gait: more useful in children over 10 years
    - Difficulty with single leg stance and “tandem stance”
    - Difficulty with feet together stance
    - Difficulty with stance with eyes closed, especially with feet together
    - Broadening of stance to maintain balance
    - Increase in inter-foot distance with walking
- No spasticity in typical FRDA in early stages: passive limb movements (typically around the knee joint) do not elicit stiffness. Atypical FRDA (late onset) may have spasticity.
- No Gowers sign
- Deep tendon reflex loss in the lower limbs (or generalized). May be normal or brisk in late onset cases
- Impaired position and vibration sense
    - Normal persons can perceive minimal movements around the distal interphalangeal joints with eyes closed
    - Normal persons can perceive minimal vibration with a 128 Hz tuning fork; one way to make this “objective” is to have subject close eyes and assess ability to distinguish between minimal vibration and no vibration over the toes, applied in a random manner
- Abnormal heel to shin slide; later, abnormal finger to nose and dysmetria tests

- Subtle oculomotor signs indicating cerebellar disease: inaccurate saccades, jerky pursuit and square wave jerks. Often no nystagmus.
- Scanning dysarthria but usually not an early sign. Patients may report speech changes when fatigued
- Brain and spine MRI typically normal (no overt cerebellar atrophy despite ataxia)
- Serum muscle enzymes are normal

Late onset Friedreich ataxia

Individuals with onset at ages above 25 or even after age 40 (very late onset) usually have neurological signs similar to those seen with classical onset FRDA, but atypical features such as prominent spasticity and lack of significant sensory neuronopathy are more common (69-73). Systemic features such as cardiomyopathy, skeletal deformities and diabetes tend not to occur. Thus, FRDA should be considered in an individual with adult onset progressive ataxia if a clear autosomal dominant history is not evident.

1.5.3 Laboratory studies

Brain MRI and spinal cord MRIs are typically normal in FRDA. While some earlier series reported cerebellar atrophy, most recent data suggest that significant cerebellar atrophy in the clinical context is not a feature of FRDA, though quantitative measures may detect subtle changes (74, 75). Volumetric data can also suggest spinal cord atrophy but this can be difficult to detect in clinical scans.

Electromyographic studies typically reveal a “pure sensory” neuropathy with loss or diminished amplitudes of sensory nerve action potentials in a generalized fashion, striking in children because they typically have very robust responses compared to adults (76). Motor nerve studies are normal, but most importantly, do not reveal conduction velocities in the “demyelinating” range (typically lower than 38 to 40 meters/sec in the upper limbs).

Over 70% of people with FRDA have subtle and non-specific ECG abnormalities such as ST segment changes and T wave inversion. Echocardiogram may show a hypertrophic cardiomyopathy.

Genetic testing for FRDA is the preferred diagnostic test. It is important to note that the GAA expansion leading to FRDA cannot be detected by next generation sequencing technology. Testing for the FRDA repeat expansion is included in some commercial genetic testing panels for ataxia. While over 96% of people with FRDA have a homozygous GAA expansion, about 3% to 4% have only one allele with the expansion, and the other has a conventional mutation. Thus, anyone with ataxia who has one expanded allele should have the other allele sequenced.

For more details, see section 1.2: Genetics and pathophysiology of FRDA, above, and Chapter 11: Genetic issues in Friedreich ataxia.

1.5.4 Disorders that share features with Friedreich ataxia in childhood

The number of disorders that lead to gait and motor difficulties in childhood is large. Thus, rarer disorders such as FRDA may not figure prominently in the differential diagnosis when a primary care physician or orthopedic surgeon evaluates these children. Such disorders range from cerebral palsy (CP), including so called “ataxic CP”, spinal dysraphic states and many neurological disorders,

including spinal cord disorders, CMT, and other inherited ataxias (77). Another common motor impairment in children has been labeled developmental coordination disorder (DCD) (78).

Inherited neuropathies such as CMT constitute a significant misdiagnosis in FRDA. Findings of imbalance resembling gait ataxia can occur in CMT. When CMT is combined with tremor (Roussy Levy syndrome) it can superficially resemble FRDA (10). Most CMT is dominantly inherited but variable penetrance may lead to misleading family history and sporadic cases can occur with recessive forms or spontaneous mutations. CMT type 1 leads to severe slowing motor nerve velocities and such a finding will exclude FRDA, as noted above.

CP typically causes symptoms before 2 years of age and delay in motor and cognitive skill development occurs very early in life. In addition, the deficits are stable and static with no regression. Spasticity is common. However, deficits related to an early static dysfunction in the brain may show some changes related to body growth and maturation of neurological function as a child grows.

DCD is characterized by impairment of motor coordination unrelated to intellectual disability and other recognized neurological disorders (78). These children usually come to medical attention before 10 years of age but the range is from 5-18 years of age, thus overlapping the age of onset of FRDA. The symptoms may involve fine movements or gross movements and either improve or persist unchanged into adult life. Common symptoms include problems with writing, drawing, dressing, pouring a drink and participation in outdoor activities.

Numerous other disorders can cause ataxic and non-ataxic motor difficulties in childhood but the distinct phenotype of FRDA should allow for easy distinction.

1.6 Overview of quality of life in Friedreich ataxia

Jennifer Farmer, Elisabetta Soragni and Myriam Rai

1.6.1 Background

Quality of life (QOL) in FRDA is influenced by many different factors, not the least of which is living with a chronic, progressive disease. Being able to quantify health-related QOL issues is essential to clinical research and long-term evaluation of the impact of new treatments and guideline recommendations. This section covers specific issues related to QOL in individuals with FRDA; in particular, techniques and equipment that promote health and independence in a person with FRDA, and the presence and management of mental health and psychological symptoms related to FRDA. Specific attention is given to medical management in the later stages of the disease process when QOL is the driving focus of medical decision making.

1.6.2 Literature review

There are only a handful of studies specifically evaluating QOL in individuals with FRDA. Findings from these studies are summarized in Table 1.4.

There is no doubt that FRDA is associated with decreased QOL. The Australian and US studies have very similar findings, utilizing the SF-36 to quantify QOL in diverse cross-sectional cohorts of adults with FRDA (89, 90). The SF-36, while not specific to FRDA, is able to capture QOL at various stages of disease (89, 90). While physical components have worse scores, both physical and mental components of health-related QOL are decreased in individuals with FRDA in various stages of disease (89, 90). Even those with milder stage and/or late onset FRDA reported decreased QOL (90).

A more recent large study in a heterogeneous cohort confirmed these observations and showed a correlation between physical scales and some disease features and their decline over time (91). When depression symptoms are analyzed, these scores are predictive of QOL (92). A study analyzing the association between mobility device use in children with FRDA and their health-related QOL shows that mobility device use is associated with worse QOL outcomes, with the effect being greatest for physical functioning (93). Worsening of academic, social, and emotional functioning also suggests that use of mobility devices has important psychosocial implications for children with FRDA. A more recent study (94) has determined an association of patient-reported vision-specific QOL with visual function and disease status in FRDA. The 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) was significantly lower (indicating worse QOL) in FRDA compared to other controls groups. Rank correlations revealed lower NEI-VFQ-25 scores among patients with greater disease severity (94).

The results from these studies should signal to a clinician that from the point of diagnosis onward individuals with FRDA may have decreased QOL, which may impact on other aspects of life including psychological function. Any adjunctive support that can improve an individual's symptoms, especially physical symptoms such as reduced ambulation, fatigue or pain, could improve QOL.

For more information, see Chapter 16: Digital and assistive technologies in Friedreich ataxia.

In reviewing QOL studies, it is important to note the range of instruments used to measure QOL in FRDA. The SF-36 (in various versions) has been used most often for adult participants (89, 90, 95). In pediatric cohorts, the PedsQL has been used to assess QOL (96, 97). This instrument offers both child report questionnaires based on age and parental report questionnaire. In addition, there has been research to develop a disease-specific instrument, the Friedreich's Ataxia Impact Scale or FAIS (98), but it has not yet been used widely.

Table 1.4 Literature review of general quality of life in Friedreich ataxia

Authors	Study type	Participants	QOL measure	Results	Conclusions
Riazi et al, 2006 (95)	Prospective, observational; questionnaire mailed to individuals at T1 – baseline and T2 – 12 months later (97% response rate)	56 individuals with FRDA (57% female; mean age 31 years)	Barthel Index (BI), General Health Questionnaire (GHQ-12), EuroQOL (EQ-5D) and SF-36 version 1	Scores on individual measures were reported for subjects but not controls or population norms.	All four generic instruments used to assess QOL were found generally suitable with some limitations. The BI and EuroQOL have several missing data points and therefore are not recommended for this population. While the subscales of the SF-36 were able to capture multiple dimensions, some of the subscales had floor and/or ceiling effects in this population. Authors argue that a disease-

Authors	Study type	Participants	QOL measure	Results	Conclusions
					specific instrument is warranted.
Wilson et al, 2007 (90)	Cross-sectional; data collected at time of visit	63 individuals with FRDA (15 years and older; 54% female and 46% male, mean age 33 years)	SF-36 V2	SF-36 V2 scores were compared with Australian population norms. Physical Component Summary – mean score 35.1, P<0.01. Mental Component Summary – mean score 48.1, P<0.01.	QOL is significantly reduced in individuals with FRDA, physical dimensions of QOL being most affected. Individuals with mild, moderate and severe disease all perceived significantly worse QOL, including those with adult onset FRDA.
Epstein et al, 2008 (89)	Cross-sectional; data collected at time of visit	130 adults with FRDA (72 females and 58 males; median age 33.5 years)	SF-36 (version 1 derived from the Multiple Sclerosis Quality of Life Inventory - MSQLI) and symptom-specific scales used in the MSQLI (Pain, Fatigue, Bladder dysfunction, Bowel dysfunction and Visual Impairment)	SF-36 scores were compared with US population norms. Physical Component Summary (mean ± standard deviation): 33.2 ± 9.3, P<0.0001. Mental Component Summary: 51.9 ± 10.0. MSQLI – Subscales of Fatigue, Pain Bladder (all P-values<0.0001) and Vision were lower in individuals with FA compared to controls.	Both the SF-36 and symptom-specific HRQOL questionnaires captured QOL especially related to physical symptoms. The Physical Component Summary and Physical Functioning Subscale of the SF-36 correlated with measures of disease progression.
Cano et al, 2009 (98)	Cross-sectional; questionnaire mailed to individuals (69% response rate)	307 individuals with reported FRDA (18 to 82 years of age; 53% female and 47% male;	Friedreich Ataxia Impact Scale (FAIS 126 item scale in full version with shortened versions for observational studies or for	Patient-reported rating scale quantifying eight areas considered clinically important to individuals with	This study validated a new FRDA-specific comprehensive measure in a large and diverse cohort of adult individuals with FRDA.

Authors	Study type	Participants	QOL measure	Results	Conclusions
		average age 40 years)	"more" or "less" severe cohorts).	FRDA: Speech, Body movement, Upper limb functioning, Lower limb functioning, Complex tasks, Mood, Self-perception, and Isolation. Rasch analysis allowed for the development of three shorter versions of the FAIS.	
Paulsen et al, 2010 (97)	Cross-sectional; data collected at time of visit	43 children with FRDA (8 to 18 years of age; 21 males and 22 females; average age 13.2 years); and parents	PedsQL 4.0 – 23-item multi-dimensional questionnaire that has been validated in healthy and chronic disease cohorts. A Generic Core Scale assessed four domains (physical, emotional, social and school) and subscale scores are derived for physical and psychosocial. Other symptom-specific scales are available, such as fatigue which was used in this study.	Child Self Report: Generic Core Total (mean ± standard deviation) - 66.4±14.7, P<0.0001. Physical Health Subscale – 63.2±17.4, P<0.0001. Psychosocial Heath Subscore – 68.1±16.2, P<0.0001. Fatigue Total Score – 72.8±15.3, P<0.01. Parental Report: Generic Core Total - 62.8±15.9, P<0.0001. Physical Health Subscale – 54.7±21.5, P<0.0001. Psychosocial Heath Subscore – 67.1±16.4, P<0.0001.	Children and parents both reported lower QOL compared to literature-based control groups. Physical health scores were the lowest. PedsQL 4.0 captures aspects of health-related QOL across multiple dimensions and demonstrates modest correlation with measures of disease severity in children with FRDA.

Authors	Study type	Participants	QOL measure	Results	Conclusions
				Fatigue Total Score – 73.2±14.0, P<0.0001.	
Brandsema et al, 2010 (96)	Prospective, observational study. Duration 1 year with use of Idebenone (no previous use of Idebenone in cohort). Data collected at baseline and 1 year follow-up.	7 children with FRDA (13 to 18 years of age; 4 males and 3 females; average age 15.9 years)	PedsQL 4.0 (see description above), Activities of Daily Living (ADL) – self-reported 11-item questionnaire that assesses function in nine categories.	PedsQL Child Self Report: Generic Core Total (mean ± standard deviation): Baseline - 46.43±19.45 and 1 year 49.00±11.34. Physical Health Subscale – 35.57±25.95 and 1 year 27.43±15.82. Emotional Subscale – Baseline 47.17±12.20 and 1 year 53.57±15.20. Changes over time were not statistically significant	This study demonstrated the use of QOL and ADL instruments in a small observational study. The baseline scores are similar to those reported in other studies demonstrating decreased QOL in children with FRDA. This study is limited in size and had no control group so definitive conclusions cannot be made about the effect of Idebenone on QOL.
Ejaz et al, 2018 (93)	Data collected from a prospective natural history study	111 pediatric FRDA patients (40.5% female; average age at assessment = 13 years average age starting using device = 11.6 years)	PedsQL 4.0, Friedreich Ataxia Rating Scale, Activities of Daily Living score, Friedreich ataxia staging score. Mobility device use was determined by a dichotomous (yes or no) question.	Physical subscore: mean = -19.5 points, 95% CI: -30.00 to -8.99, P<0.001 Emotional subscore: mean = -10.61 points, 95% CI: -20.21 to 1.02, P=0.03 Transition to or between mobility devices: mean = -16.20 points, 95% CI: -32.07 to -0.33, P=0.05	Mobility device use is associated with worse mean PedsQL total, physical, emotional, social, and academic subscores. The magnitude of the difference was greatest for the physical subscore and least for the emotional subscore. Transition to or between mobility devices trended toward worse physical subscore
Xiong et al, 2020 (91)	Data collected from a	SF-36: 651 adult subjects	SF-36	Social function (mean ±	Cross sectional data show the physical

Authors	Study type	Participants	QOL measure	Results	Conclusions
	prospective natural history study	(mean ± standard deviation age = 32.4 ± 12.8 years Symptom-specific scales testing: 805 subjects (mean ± standard deviation age = 32.4 ± 13.6 years).	Specific symptoms assessed included pain (Pain Effects Scale, PES), bladder dysfunction (Bladder Control Scale, BLCS), fatigue (Modified Fatigue Impairment Scale), and visual impairment (Impact of Visual Impairment Scale)	standard deviation) 65.0 ± 26.7 Role-physical 43.0 ± 39.6 Role-emotional 68.6 ± 40.2 Physical function 26.1 ± 25.9 Pain 68.1 ± 24.3 Energy fatigue 47.8 ± 20.5 General health 52.9 ± 20.9 Emotional 69.0 ± 18.5	function scale to be the lowest score, with higher scores on social, cognitive and emotional subscores. Physical function, role limitation score and symptom specific scores declined over time SF-36 and symptom-specific scales correlate with some disease features
Pérez-Flores et al, 2020 (92)	Cross-sectional; questionnaires self-administered and data collected at time of visit	62 adults with FRDA (mean age ± standard deviation = 40.98 ± 13.52)	SF-36 BDI-II (Beck Depression Inventory)	SF-36 dimensions scores significantly lower in FRDA than in the Spanish population: Physical function (mean ± standard deviation) 15.81 ± 19.98 Role-physical 41.53 ± 43.16 Body pain 60.44 ± 29.39 General Health 35.32 ± 21.33 Vitality 52.10 ± 23.83 Social function 65.93 ± 29.53 Role-emotional 70.97 ± 41.59	High impact of FRDA on QOL. This impact occurs in both motor disability and non-motor dimensions. Depression is the most relevant variable for predicting QOL. Recognition and treatment of depression are essential to improve the subjective experience of QOL in FRDA.

Authors	Study type	Participants	QOL measure	Results	Conclusions
				Mental Health 64.84 ± 22.36 BDI-II 15.32 ± 10.33 BDI-II scores negatively related to all SF-36 dimensions except for Physical function Depression accounted for variance of: 6% of role-physical and Body pain 18% of Vitality 26% of Social function 51% of Mental Health	
Afsharian et al, 2020 (94)	Cross-sectional study, questionnaires self-administered and collected at time of visit for a natural history study	99 individuals with FRDA (mean ± standard deviation age = 57.3 ± 20.9)	National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25)	NEI-VFQ-25 scores are lower in FRDA than in controls: mean ± standard deviation = 86.4 ± 19.2 Most affected subscores are: General Health 58.0 ± 24.0 General vision 80.0 ± 21.4 Distance vision 81.8 ± 24.3 Peripheral vision 82.6 ± 26.6 FRDA patients with lower scores were	NEI-VFQ-25 is an appropriate patient-reported measure of vision-specific QOL in FRDA NEI-VFQ-25 scores worsen as FRDA progresses and as visual dysfunction becomes more severe.

Authors	Study type	Participants	QOL measure	Results	Conclusions
				older and had greater severity of neurological and visual dysfunctions.	

Author details

Sanjay I. Bidichandani, MBBS, PhD
Professor of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
Email: sanjay-bidichandani@ouhsc.edu

Antoine Duquette, MD, MSc, FRCP(C)
Associate Clinical Professor, Centre hospitalier de l'Université de Montréal, Montréal, Québec, Canada
Email: antoine.duquette@umontreal.ca

Jennifer Farmer, MS
Chief Executive Officer, Friedreich's Ataxia Research Alliance (FARA), Downingtown, Pennsylvania, USA
Email: info@curefa.org

Marcondes C. França Jr, MD, PhD
Associate Professor, Department of Neurology, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil
Email: mcfjr@unicamp.br

Arnulf H. Koeppen, MD
Research Physician, Veterans Affairs Medical Center, Albany, New York, USA
Email: arnulf.koeppen@med.va.gov

Katherine Mathews, MD
Professor, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA
Email: katherine-mathews@uiowa.edu

Hélène Puccio, PhD
Research Director Inserm, Institut Neuromyogène - Pathophysiology and Genetics of Neuron and Muscle, Lyon, France
Email: helene.puccio@inserm.fr

Myriam Rai, PhD
Director of Global Relations & Initiatives, Friedreich's Ataxia Research Alliance (FARA), Brussels, Belgium
Email: myriam.rai@curefa.org

Kathrin Reetz, MD
Professor for Translational Neurodegeneration, Department of Neurology, RWTH Aachen University, Aachen, NRW, Germany
Email: kreetz@ukaachen.de

Ludger Schöls, MD
Professor of Neurology, Eberhard-Karls University, Tübingen, Germany
Email: Ludger.Schoels@uni-tuebingen.de

Elisabetta Soragni
Director of Research, The Friedreich's Ataxia Research Alliance, Downingtown, Pennsylvania, USA
Email: liz.soragni@curefa.org

Sub H. Subramony, MD
Professor of Neurology and Pediatrics, University of Florida College of Medicine, Gainesville, Florida, USA
Email: s.subramony@neurology.ufl.edu

Ariane Veilleux Carpentier, MD
Neurology Resident, Université de Montréal, Montréal, Québec, Canada

Robert B. Wilson, MD, PhD
Professor of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
Email: wilsonr@pennmedicine.upenn.edu

References

1. Brousse M. De l'ataxie héréditaire: Thèse de Montpelier; 1882.
2. Friedreich N. Uber degenerative Atrophie der spinalen Hinterstrange. Virchow's Arch Path Anat. 1863;26:291-419.
3. Friedreich N. Uber degenerative Atrophie der spinalen Hinterstrange. Virchow's Arch Path Anat. 1863;27:1-26.
4. Friedreich N. Uber degenerative Atrophie der spinalen Hinterstrange. Virchow's Arch Path Anat. 1863;26:433-59.
5. Friedreich N. Uber ataxie mit besonderer berucksichtigung der herditaren formen. Virchow's Arch Path Anat. 1876;68:145-245.
6. Friedreich N. Uber ataxie mit besonderer berucksichtigung der hereditaren formen. Virchow's Arch Path Anat. 1877;70:140-52.
7. Campuzano V, Montermini L, Molto MD, Pianese L, Cossee M, Cavalcanti F, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science. 1996;271(5254):1423-7.
8. Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol. 2015;14(2):174-82.
9. Geoffroy G, Barbeau A, Breton G, Lemieux B, Aube M, Leger C, et al. Clinical description and roentgenologic evaluation of patients with Friedreich's ataxia. Can J Neurol Sci. 1976;3(4):279-86.
10. Harding AE. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. Brain. 1981;104(3):589-620.
11. Dürr A, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. N Engl J Med. 1996;335(16):1169-75.
12. Schöls L, Amoiridis G, Przuntek H, Frank G, Epplen JT, Epplen C. Friedreich's ataxia. Revision of the phenotype according to molecular genetics. Brain. 1997;120(Pt 12):2131-40.
13. Bürk K. Friedreich ataxia: current status and future prospects. Cerebellum Ataxias. 2017;4:4.
14. Rummey C, Farmer JM, Lynch DR. Predictors of loss of ambulation in Friedreich's ataxia. EClinicalMedicine. 2020;18:100213.

15. Delatycki MB, Paris DB, Gardner RJ, Nicholson GA, Nassif N, Storey E, et al. Clinical and genetic study of Friedreich ataxia in an Australian population. Am J Med Genet. 1999;87(2):168-74.
16. Rosen KM, Folker JE, Vogel AP, Corben LA, Murdoch BE, Delatycki MB. Longitudinal change in dysarthria associated with Friedreich ataxia: a potential clinical endpoint. J Neurol. 2012;259(11):2471-7.
17. Ribaï P, Pousset F, Tanguy M, Rivaud-Pechoux S, Le Ber I, Gasparini F, et al. Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up. Arch Neurol. 2007;64:558-64.
18. Patel M, Isaacs CJ, Seyer L, Brigatti K, Gelbard S, Strawser C, et al. Progression of Friedreich ataxia: quantitative characterization over 5 years. Ann Clin Transl Neurol. 2016;3(9):684-94.
19. Delatycki MB, Corben LA. Clinical features of Friedreich ataxia. J Child Neurol. 2012;27(9):1133-7.
20. Musegante A, Almeda P, Monteiro R, Bassoro U. Urinary symptoms and urodynamics findings in patients with Friedreich's ataxia. International Brazilian Journal of Urology. 2013;39(6):867-74.
21. McCabe DJ, Ryan F, Moore DP, McQuaid S, King MD, Kelly A, et al. Typical Friedreich's ataxia without GAA expansions and GAA expansion without typical Friedreich's ataxia.[erratum appears in J Neurol 2000 Jun;247(6):483]. J Neurol. 2000;247(5):346-55.
22. Tsou AY, Paulsen EK, Lagedrost SJ, Perlman SL, Mathews KD, Wilmot GR, et al. Mortality in Friedreich ataxia. J Neurol Sci. 2011;307:46-9.
23. Pousset F, Legrand L, Monin ML, Ewenczyk C, Charles P, Komajda M, et al. A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia. JAMA Neurol. 2015;72(11):1334-41.
24. Fortuna F, Barboni P, Liguori R, Valentino ML, Savini G, Gellera C, et al. Visual system involvement in patients with Friedreich's ataxia. Brain. 2009;132(Pt 1):116-23.
25. Rance G, Fava R, Baldock H, Chong A, Barker E, Corben L, et al. Speech perception ability in individuals with Friedreich ataxia. Brain. 2008;131:2002-12.
26. Galea CA, Huq A, Lockhart PJ, Tai G, Corben LA, Yiu EM, et al. Compound heterozygous FXN mutations and clinical outcome in Friedreich ataxia. Ann Neurol. 2016;79(3):485-95.
27. Colombo R, Carobene A. Age of the intronic GAA triplet repeat expansion mutation in Friedreich ataxia. Hum Genet. 2000;106(4):455-8.
28. Campuzano V, Montermini L, Lutz Y, Cova L, Hindelang C, Jiralerspong S, et al. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. Hum Mol Genet. 1997;6(11):1771-80.
29. Li Y, Lu Y, Polak U, Lin K, Shen J, Farmer J, et al. Expanded GAA repeats impede transcription elongation through the FXN gene and induce transcriptional silencing that is restricted to the FXN locus. Hum Mol Genet. 2015;24(24):6932-43.
30. Rodden LN, Chutake YK, Gilliam K, Lam C, Soragni E, Hauser L, et al. Methylated and unmethylated epialleles support variegated epigenetic silencing in Friedreich ataxia. Hum Mol Genet. 2021;29(23):3818-29.
31. Herman D, Jenssen K, Burnett R, Soragni E, Perlman SL, Gottesfeld JG. Histone deacetylase inhibitors reverse gene silencing in Friedreich's ataxia. Nat Chem Biol. 2006;2(10):551-8.
32. Li L, Matsui M, Corey DR. Activating frataxin expression by repeat-targeted nucleic acids. Nat Commun. 2016;7:10606.
33. Gervason S, Larkem D, Mansour AB, Botzanowski T, Muller CS, Pecqueur L, et al. Physiologically relevant reconstitution of iron-sulfur cluster biosynthesis uncovers persulfide-processing functions of ferredoxin-2 and frataxin. Nat Commun. 2019;10(1):3566.
34. Gonzalez-Cabo P, Palau F. Mitochondrial pathophysiology in Friedreich's ataxia. J Neurochem. 2013;126 Suppl 1:53-64.
35. Koeppen AH. Friedreich's ataxia: pathology, pathogenesis, and molecular genetics. J Neurol Sci. 2011;303(1-2):1-12.
36. Harding IH, Lynch DR, Koeppen AH, Pandolfo M. Central nervous system therapeutic targets in Friedreich ataxia. Hum Gene Ther. 2020;31(23-24):1226-36.

37. Koeppen AH, Becker AB, Qian J, Feustel PJ. Friedreich Ataxia: Hypoplasia of Spinal Cord and Dorsal Root Ganglia. J Neuropathol Exp Neurol. 2017;76(2):101-8.
38. Koeppen AH, Becker AB, Qian J, Gelman BB, Mazurkiewicz JE. Friedreich Ataxia: Developmental Failure of the Dorsal Root Entry Zone. J Neuropathol Exp Neurol. 2017;76(11):969-77.
39. Dogan I, Romanzetti S, Didszun C, Mirzazade S, Timmann D, Saft C, et al. Structural characteristics of the central nervous system in Friedreich ataxia: an in vivo spinal cord and brain MRI study. J Neurol Neurosurg Psychiatry. 2019;90(5):615-7.
40. Dogan I, Tinnemann E, Romanzetti S, Mirzazade S, Costa AS, Werner CJ, et al. Cognition in Friedreich's ataxia: a behavioral and multimodal imaging study. Ann Clin Transl Neurol. 2016;3(8):572-87.
41. Lindig T, Bender B, Kumar VJ, Hauser TK, Grodd W, Brendel B, et al. Pattern of cerebellar atrophy in Friedreich's ataxia-using the SUIT template. Cerebellum. 2019;18(3):435-47.
42. Rezende TJR, Martinez ARM, Faber I, Girotto Takazaki KA, Martins MP, de Lima FD, et al. Developmental and neurodegenerative damage in Friedreich's ataxia. Eur J Neurol. 2019;26(3):483-9.
43. Selvadurai LP, Corben LA, Delatycki MB, Storey E, Egan GF, Georgiou-Karistianis N, et al. Multiple mechanisms underpin cerebral and cerebellar white matter deficits in Friedreich ataxia: The IMAGE-FRDA study. Hum Brain Mapp. 2020;41(7):1920-33.
44. Vavla M, Arrigoni F, Nordio A, De Luca A, Pizzighello S, Petacchi E, et al. Functional and structural brain damage in Friedreich's ataxia. Front Neurol. 2018;9:747.
45. Ward PGD, Harding IH, Close TG, Corben LA, Delatycki MB, Storey E, et al. Longitudinal evaluation of iron concentration and atrophy in the dentate nuclei in friedreich ataxia. Mov Disord. 2019;34(3):335-43.
46. Gramegna LL, Tonon C, Manners DN, Pini A, Rinaldi R, Zanigni S, et al. Combined cerebellar proton MR spectroscopy and DWI study of patients with Friedreich's ataxia. Cerebellum. 2017;16(1):82-8.
47. Öz G, Harding IH, Krahe J, Reetz K. MR imaging and spectroscopy in degenerative ataxias: toward multimodal, multisite, multistage monitoring of neurodegeneration. Curr Opin Neurol. 2020;33(4):451-61.
48. Cocozza S, Costabile T, Tedeschi E, Abate F, Russo C, Liguori A, et al. Cognitive and functional connectivity alterations in Friedreich's ataxia. Ann Clin Transl Neurol. 2018;5(6):677-86.
49. Survey of the delay in diagnosis for 8 rare diseases in Europe ('EurordisCare2') 2007 [Available from: https://www.eurordis.org/publication/survey-delay-diagnosis-8-rare-diseases-europe-'eurordiscare2'.
50. Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease. Ending the diagnostic odyssey for children with a rare disease: Global Commission year one report 2019 [Available from: https://www.globalrarediseasecommission.com/Report/.
51. Indelicato E, Nachbauer W, Eigentler A, Amprosi M, Matteucci Gothe R, Giunti P, et al. Onset features and time to diagnosis in Friedreich's Ataxia. Orphanet J Rare Dis. 2020;15(1):198.
52. Filla A, De Michele G, Coppola G, Federico A, Vita G, Toscano A, et al. Accuracy of clinical diagnostic criteria for Friedreich's ataxia. Mov Disord. 2000;15(6):1255-8.
53. Filla A, De Michele G, Cavalcanti F, Pianese L, Monticelli A, Campanella G, et al. The relationship between trinucleotide (GAA) repeat length and clinical features in Friedreich ataxia. Am J Hum Genet. 1996;59(3):554-60.
54. Filla A, DeMichele G, Caruso G, Marconi R, Campanella G. Genetic data and natural history of Friedreich's disease: a study of 80 Italian patients. J Neurol. 1990;237(6):345-51.
55. De Michele G, Di Maio L, Filla A, Majello M, Cocozza S, Cavalcanti F, et al. Childhood onset of Friedreich ataxia: a clinical and genetic study of 36 cases. Neuropediatrics. 1996;27(1):3-7.
56. Hanna MG, Davis MB, Sweeney MG, Noursadeghi M, Ellis CJ, Elliot P, et al. Generalized chorea in two patients harboring the Friedreich's ataxia gene trinucleotide repeat expansion. Mov Disord. 1998;13(2):339-40.

57. Spacey SD, Szczygielski BI, Young SP, Hukin J, Selby K, Snutch TP. Malaysian siblings with friedreich ataxia and chorea: a novel deletion in the frataxin gene. Can J Neurol Sci. 2004;31(3):383-6.
58. Zhu D, Burke C, Leslie A, Nicholson GA. Friedreich's ataxia with chorea and myoclonus caused by a compound heterozygosity for a novel deletion and the trinucleotide GAA expansion. Mov Disord. 2002;17(3):585-9.
59. Rummey C, Corben LA, Delatycki MB, Subramony SH, Bushara K, Gomez CM, et al. Psychometric properties of the Friedreich Ataxia Rating Scale. Neurology Genetics. 2019;5(6):371.
60. Furman JM, Perlman S, Baloh RW. Eye movements in Friedreich's ataxia. Arch Neurol. 1983;40(6):343-6.
61. Kirkham TH, Guitton D, Katsarkas A, Kline LB, Andermann E. Oculomotor abnormalities in Friedreich's ataxia. Can J Neurol Sci. 1979;6(2):167-72.
62. Ell J, Prasher D, Rudge P. Neuro-otological abnormalities in Friedreich's ataxia. J Neurol Neurosurg Psychiatry. 1984;47(1):26-32.
63. Lamont PJ, Davis MB, Wood NW. Identification and sizing of the GAA trinucleotide repeat expansion of Friedreich's ataxia in 56 patients. Clinical and genetic correlates. Brain. 1997;120(Pt 4):673-80.
64. Konieczny MR, Senyurt H, Krauspe R. Epidemiology of adolescent idiopathic scoliosis. J Child Orthop. 2013;7(1):3-9.
65. Allam AM, Schwabe AL. Neuromuscular scoliosis. PM R. 2013;5(11):957-63.
66. Mary P, Servais L, Vialle R. Neuromuscular diseases: Diagnosis and management. Orthop Traumatol Surg Res. 2018;104(1S):S89-S95.
67. Ahluwalia M, Ho CY. Cardiovascular genetics: the role of genetic testing in diagnosis and management of patients with hypertrophic cardiomyopathy. Heart. 2021;107(3):183-9.
68. Stafford F, Thomson K, Butters A, Ingles J. Hypertrophic cardiomyopathy: Genetic testing and risk stratification. Curr Cardiol Rep. 2021;23(2):9.
69. Berciano J, Mateo I, De Pablos C, Polo JM, Combarros O. Friedreich ataxia with minimal GAA expansion presenting as adult-onset spastic ataxia. J Neurol Sci. 2002;194(1):75-82.
70. Bhidayasiri R, Perlman SL, Pulst SM, Geschwind DH. Late-onset Friedreich ataxia: phenotypic analysis, magnetic resonance imaging findings, and review of the literature. Arch Neurol. 2005;62(12):1865-9.
71. Fearon C, Lonergan R, Ferguson D, Byrne S, Bradley D, Langan Y, et al. Very-late-onset Friedreich's ataxia: diagnosis in a kindred with late-onset cerebellar ataxia. Pract Neurol. 2020;20(1):55-8.
72. Lhatoo SD, Rao DG, Kane NM, Ormerod IE. Very late onset Friedreich's presenting as spastic tetraparesis without ataxia or neuropathy. Neurology. 2001;56(12):1776-7.
73. Lecocq C, Charles P, Azulay JP, Meissner W, Rai M, N'Guyen K, et al. Delayed-onset Friedreich's ataxia revisited. Mov Disord. 2016;31(1):62-9.
74. Schulz JB, Boesch S, Burk K, Durr A, Giunti P, Mariotti C, et al. Diagnosis and treatment of Friedreich ataxia: a European perspective. Nat Rev Neurol. 2009;5(4):222-34.
75. Selvadurai LP, Harding IH, Corben LA, Georgiou-Karistianis N. Cerebral abnormalities in Friedreich ataxia: A review. Neurosci Biobehav Rev. 2018;84:394-406.
76. Caruso G, Santoro L, Perretti A, Serlenga L, Crisci C, Ragno M, et al. Friedreich's ataxia: electrophysiological and histological findings. Acta Neurol Scand. 1983;67(1):26-40.
77. Michel C, Collins C. Pediatric neuromuscular disorders. Pediatr Clin North Am. 2020;67(1):45-57.
78. Spittle AJ, FitzGerald T, Mentiplay B, Williams J, Licari M. Motor impairments in children: More than just the clumsy child. J Paediatr Child Health. 2018;54(10):1131-5.
79. Mateo I, Llorca J, Volpini V, Corral J, Berciano J, Combarros O. Expanded GAA repeats and clinical variation in Friedreich's ataxia. Acta Neurol Scand. 2004;109(1):75-8.
80. Al-Mahdawi S, Ging H, Bayot A, Cavalcanti F, La Cognata V, Cavallaro S, et al. Large Interruptions of GAA Repeat Expansion Mutations in Friedreich Ataxia Are Very Rare. Front Cell Neurosci. 2018;12:443.

81. Berciano J, Mateo I, De Pablos C, Polo JM, Combarros O. Friedreich ataxia with minimal GAA expansion presenting as adult-onset spastic ataxia. J Neurol Sci. 2002;194(1):75-82.
82. Napierala M, Dere R, Vetcher A, Wells RD. Structure-dependent recombination hot spot activity of GAA.TTC sequences from intron 1 of the Friedreich's ataxia gene. J Biol Chem. 2004;279(8):6444-54.
83. Bit-Avragim N, Perrot A, Schols L, Hardt C, Kreuz FR, Zuhlke C, et al. The GAA repeat expansion in intron 1 of the frataxin gene is related to the severity of cardiac manifestation in patients with Friedreich's ataxia. J Mol Med. 2001;78(11):626-32.
84. Isnard R, Kalotka H, Durr A, Cossee M, Schmitt M, Pousset F, et al. Correlation between left ventricular hypertrophy and GAA trinucleotide repeat length in Friedreich's ataxia. Circulation. 1997;95(9):2247-9.
85. Marty B, Naeije G, Bourguignon M, Wens V, Jousmaki V, Lynch DR, et al. Evidence for genetically determined degeneration of proprioceptive tracts in Friedreich ataxia. Neurology. 2019;93(2):e116-e24.
86. Monrós E, Molto MD, Martinez F, Canizares J, Blanca J, Vilchez JJ, et al. Phenotype correlation and intergenerational dynamics of the Friedreich ataxia GAA trinucleotide repeat. Am J Hum Genet. 1997;61(1):101-10.
87. Greeley NR, Regner S, Willi S, Lynch DR. Cross-sectional analysis of glucose metabolism in Friedreich ataxia. J Neurol Sci. 2014;342(1-2):29-35.
88. Cossée M, Dürr A, Schmitt M, Dahl N, Trouillas P, Allinson P, et al. Friedreich's ataxia: point mutations and clinical presentation of compound heterozygotes. Ann Neurol. 1999;45(2):200-6.
89. Epstein E, Farmer JM, Tsou A, Perlman S, Subramony SH, Gomez CM, et al. Health related quality of life measures in Friedreich Ataxia. J Neurol Sci. 2008;272(1-2):123-8.
90. Wilson C, Fahey MC, Corben L A, Collins V, Churchyard A, Lamont PJ, et al. Quality of life in Friedreich Ataxia: what clinical, social and demographic factors are important? Eur J Neurol. 2007;14(9):1040-7.
91. Xiong E, Lynch AE, Corben LA, Delatycki MB, Subramony SH, Bushara K, et al. Health related quality of life in Friedreich Ataxia in a large heterogeneous cohort. J Neurol Sci. 2020;410:116642.
92. Perez-Flores J, Hernandez-Torres A, Monton F, Nieto A. Health-related quality of life and depressive symptoms in Friedreich ataxia. Qual Life Res. 2020;29(2):413-20.
93. Ejaz R, Chen S, Isaacs CJ, Carnevale A, Wilson J, George K, et al. Impact of mobility device use on quality of life in children with Friedreich ataxia. J Child Neurol. 2018;33(6):397-404.
94. Afsharian P, Nolan-Kenney R, Lynch AE, Balcer LJ, Lynch DR. Correlation of visual quality of life with clinical and visual status in Friedreich ataxia. J Neuroophthalmol. 2020;40(2):213-7.
95. Riazi A, Cano SJ, Cooper JM, Bradley JL, Schapira AH, Hobart JC. Coordinating outcomes measurement in ataxia research: do some widely used generic rating scales tick the boxes? Mov Disord. 2006;21(9):1396-403.
96. Brandsema JF, Stephens D, Hartley J, Yoon G. Intermediate-dose idebenone and quality of life in Friedreich ataxia. Pediatr Neurol. 2010;42(5):338-42.
97. Paulsen EK, Friedman LS, Myers LM, Lynch DR. Health-related quality of life in children with Friedreich ataxia. Pediatr Neurol. 2010;42(5):335-7.
98. Cano SJ, Riazi A, Schapira AH, Cooper JM, Hobart J. Friedreich's ataxia impact scale: a new measure striving to provide the flexibility required by today's studies. Mov Disord. 2009;24(7):984-2.