Friedreich Ataxia Backgrounder

and Important Considerations

Information that may help you manage your patients with FA

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WHAT IS FRIEDREICH ATAXIA?

Friedreich ataxia (FA) is an autosomal-recessive, neurodegenerative disease that primarily affects the nervous system but can have multisystemic effects, including cardiomyopathy. People with this disease develop impaired muscle coordination (ataxia) that worsens over time. Though rare, FA is the most common inherited ataxia.[1]

Most patients begin to experience symptoms around puberty (10 to 15 years of age). While presentation of the disease is different in every patient, gait ataxia and general clumsiness are the most common presenting symptoms.[2]

Because of the serious consequences of the disease, patients should be diagnosed as early as possible. An early diagnosis can help manage the symptoms of FA and allow for the building of a multidisciplinary care team tailored to a patient's individual needs.

The latest research in FA

The Collaborative Clinical Research Network in Friedreich's Ataxia (CCRN in FA) is an international network of clinical research centers that work together to allow patients with FA to enroll and participate in research studies and to receive clinical care. While not necessarily involved in day-to-day patient care, CCRN can be a critical resource for patients and neurologists alike. FA specialists at the CCRN have experience working with hundreds of patients with FA, can provide updates on the latest FA research, and can share information on therapies currently in development.

To learn more, visit CureFA.org/network.

FARA Friedreich's Ataxia Research Alliance

A Closer Look at Common Symptoms of FA

When ataxia is discussed, often a lack of muscle coordination comes to mind. However, it is important to note that FA can also manifest in other ways. Some of the main symptoms observed in patients with FA are outlined below.

Reflexes, muscle tone, and sensory loss[2]

- Loss of reflexes, particularly in the lower limbs, and extensor plantar reactions are present in almost all patients
- Muscle tone is typically normal or reduced, particularly in the early stages of the disease
- Spasticity occurs in some patients, particularly in the lower limbs. If left untreated, it can cause pain, discomfort, positioning problems, and contractures
- Distal sensory loss is a universal symptom, with most patients losing the ability to sense vibration and joint position

Gait and limb ataxia[2]

- When limb ataxia is present (an early feature of the disease), daily activities that require fine dexterity become much harder for patients. This causes difficulty with handwriting, washing, dressing, and use of cutlery
- As the disease progresses, there is an increasing dependence on walking aids. Initially, patients depend on furniture, walls, and other people for support. Later on, they rely on canes, crutches, and wheeled walkers
- Truncal ataxia results in swaying when sitting and may necessitate back support

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A Closer Look at Common Symptoms of FA
(cont'd)

Cardiac involvement

- While a majority of patients with FA will have evidence of cardiac complications (including cardiomyopathy and arrhythmias), patients are often asymptomatic. Palpitations are sometimes reported but overt symptoms of heart failure are uncommon[2]
- Heart disease in patients with FA can be severe and may contribute to disability and premature death. This is especially true in early-onset cases[1]
- Heart failure and arrhythmias (supraventricular in origin) are the most commonly reported causes of death[1]

Diabetes mellitus/Hyperglycemia[3,4]

- When compared with age-matched populations, diabetes is more prevalent in patients with FA—with incidence estimates varying between 8% and 32%. Younger age at onset with longer disease duration places patients at an increased risk for diabetes

Speech and swallowing

- Dysarthria is present in more than 90% of patients with FA. Over time, speech becomes slow and slurred, and patients become harder to understand in more advanced stages[2]
- As the disease progresses, dysphagia can become problematic, occasionally requiring gastroesophageal tube insertion. Patients may cough or choke on solids or liquids (including saliva), and chewing may be compromised. In some patients, this requires avoidance of tough foods, cutting food into small pieces, or increasing the bolus viscosity of liquids[2,4]

Skeletal abnormalities

- When assessed clinically, scoliosis is present in approximately two-thirds of individuals with FA, a number that increases to 100% when assessed radiographically[5]
- Scoliosis is common early in FA—particularly when a patient has a poor recovery from scoliosis surgery or presents subtle neurological signs during or after surgery[2]
- The most rapid progression of scoliosis occurs between the ages of 10 and 16, corresponding to the age of puberty, and is associated with significant growth[4,6]
- Between 55% and 90% of patients with FA have foot deformities—including cases of both high arch and clubfoot. Clubfoot is a progressive condition found in advanced disease and can be very disabling with respect to mobility, transfers, and seating[2]

Muscle weakness and wasting[2]

- Weakness occurs later in the course of the disease and is more prominent in the lower limbs compared with the upper limbs
  - Many patients preserve upper limb strength even when a wheelchair becomes necessary. Some patients may only ever develop mild distal upper limb weakness
- A significant number of patients experience wasting, and for patients who develop the disease in early life, muscle mass may never fully develop

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A Closer Look at Common Symptoms of FA
(cont'd)

Ophthalmic features[2]

- Abnormal eye movement is a common early sign in the course of FA, with fixation instability being the most common feature. Nystagmus is less common but still frequent
- Decreased visual acuity is less common than eye movement abnormality, and the majority of patients are asymptomatic
  - On occasion, however, sudden bilateral loss of vision has been observed, mimicking Leber's hereditary optic atrophy

Hearing[2]

- Most patients show disordered neural conduction in the central auditory pathways. This results in patients having trouble understanding speech in situations with everyday background noise

Bladder[2,5]

- Symptoms of bladder hyperactivity are common in FA and are exacerbated by mobility problems

Progression and mortality

- The mean duration of time from disease onset to use of a wheelchair is 15.5 years. On average, wheelchair use begins at 25 years of age[2]
- Symptoms such as dysarthria, lower limb pyramidal weakness, distal upper limb wasting, and loss of vibrational and joint position sense appear as the disease progresses[2]
- The largest retrospective study of mortality in FA included 61 individuals who had died[2]
  - Mean age at death was 36.5 years
  - Cardiac or probable cardiac dysfunction accounted for 62% of deaths. Of these, the majority resulted from heart failure or arrhythmia
- Survival into the sixth and seventh decades has been documented[5]

The table on the next page outlines the major clinical and genetic features that distinguish FA from other ataxias.

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Clinical and Genetic Features[1,2,7-12]

The information listed in the table below may be useful when trying to distinguish between the different types of ataxia.

Main clinical and genetic features of Friedreich ataxia and other neurological disorders with similar clinical characteristics

FEATURE	FRIEDREICH ATAXIA	ATAXIA TELANGIECTASIA	ATAXIA WITH OCULOMOTOR APRAXIA TYPE 1	ATAXIA WITH OCULOMOTOR APRAXIA TYPE 2	AUTOSOMAL RECESSIVE SPASTIC ATAXIA OF CHARLEVOIX–SAGUENAY	CHARCOT-MARIE-TOOTH DISEASE TYPE 1 (CMT1)*
Usual age of onset	<20 years (range, 2 years to >50 years)	<5 years (range, 2 years to 30 years)	<7 years (range, 2 years to young adult)	10-22 years	12-18 months (might occur later outside Québec)	5-25 years
Cerebellar atrophy	Present only in advanced cases	Present	Present	Present	Present	Absent (rare in Western world)
Pyramidal signs	Frequent	Present	Absent	Sometimes present	Present	Present
Peripheral neuropathy	Present (sensory axonal)	Present (axonal)	Present (motor and sensory axonal)	Present (motor and sensory axonal)	Present	Present
Other signs and symptoms	Kyphoscoliosis; pes cavus; optic atrophy; hearing difficulties; diabetes	Oculomotor apraxia; tremor; dystonia, telangiectasias of the conjunctiva; frequent sinopulmonary infections	Oculomotor apraxia; chorea; dystonia	Oculomotor apraxia; dystonia; chorea; tremor; cognitive impairment	Myelinated optic nerve fibers in the retina; scoliosis; pes cavus	Progressive distal muscle weakness; atrophy often associated with mild to moderate sensory loss; depressed tendon reflexes, bone deformities; pes cavus
Cardiomyopathy	Present	Absent	Absent	Absent	Absent (but mitral valve prolapse common)	Absent
Gene and nature of mutations	*FXN*; *GAA* repeat expansion, rare point mutations (always in heterozygosity with *GAA* repeat expansion)	*ATM*; nonsense mutations, frameshift, missense and leaky splice-site mutations, insertions and deletions	*APTX*; missense, nonsense, frameshift and splice-site mutations	*SETX*; loss-of-function missense, nonsense and truncating mutations; large-scale rearrangements	*SACS*; missense mutations, deletions and insertions	*PMP22*; duplication; point mutations

*Inherited in an autosomal dominant pattern.

FXN, frataxin; GAA, glucosidase alpha, acid; ATM, ataxia-telangiectasia mutated; APTX, aprataxin; SETX, senataxin; SACS, sacsin; PMP22, peripheral myelin protein 22.

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Multidisciplinary Specialists

Care Team Roles and Responsibilities

FA is a complex condition with variable clinical phenotypes that often require a broad multidisciplinary approach focusing on symptom management. Assembling the right care team will vary based on a patient's specific needs and circumstances.[3]

Below is a list of specialists who may play a role in helping to provide specialized care to patients with FA.

Genetic counselor[13]

When considering an FA diagnosis, a geneticist can help patients undergo genetic testing for the disease and provide counseling to the patient and family, including discussions about risks for other family members or the patient, and what it could mean for family planning.

They also provide guidance to treating physicians in terms of ordering appropriate tests and helping interpret complicated test results.

Primary care physician

The primary care physician provides consistent care for FA patients in all healthcare needs not directly related to FA. They can screen for FA complications, including cardiovascular issues, diabetes, and scoliosis.

Cardiologist[13]

Patients with FA experience a high number of cardiac symptoms and can be diagnosed with cardiomyopathy. Clinical management guidelines recommend that a cardiologist perform an electrocardiogram and an echocardiogram at the time of diagnosis, then at least once a year and provide treatment as necessary. Due to the increased risk of arrhythmia, there is a potential need for care from a cardiac electrophysiologist.

Endocrinologist[13]

The endocrinologist screens for glucose intolerance to establish a baseline in all patients with FA. They can also help counsel patients with impaired glucose tolerance or diabetes on the importance of lifestyle changes and prescribe treatment to control blood sugar levels, if necessary

Pulmonologist[13,14]

Pulmonologists can provide treatment options to help keep patients' lungs working optimally.

Ophthalmologist/Audiologist

Ophthalmologists and audiologists can perform a comprehensive vision screening and auditory evaluation, and can provide tools and support to improve day-to-day hearing or visual issues.

Orthopedic surgeon[13]

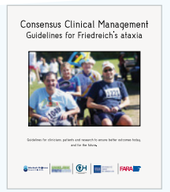
Should orthopedic complications arise, orthopedic surgeons can help recommend the best course of action for musculoskeletal symptoms of patients with FA.

Physical/Occupational therapist

Physical and occupational therapists can evaluate and optimize functional abilities and identify ways for patients to accomplish everyday tasks.

Other specialists who can help your patients:

- Physicians
- Podiatrists
- Speech therapists
- Nutritionists
- Palliative care teams
- Social workers



Learn more about managing patients with FA

Consensus clinical management guidelines for Friedreich ataxia are available on the Friedreich's Ataxia Research Alliance (FARA) website. FARA is an organization focused on research and awareness for FA.

To review the guidelines, visit CureFA.org/clinical-care-guidelines.

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Get Connected to the FA Community

Despite there being a small number of FA patients across the country, various networks exist to bring together patients, clinicians, and researchers.

Friedreich's Ataxia Research Alliance (FARA) is dedicated to scientific research. The alliance raises funds for FA research, promotes public awareness, and brings together patients, clinicians, and other organizations with an FA-related focus. Research funded by FARA has led to a better understanding of gene mutation, frataxin production, iron sulfur cluster formation, and mitochondrial dysfunction.

To learn more, visit CureFA.org.

Muscular Dystrophy Association (MDA) is committed to improving the lives of people with muscular dystrophy and other neuromuscular diseases through innovations in science and care. FA is one of the 40 disorders addressed by the association. MDA's 230 hospital-affiliated clinics offer quality multidisciplinary care from doctors, nurses, and therapists experienced in dealing with neuromuscular diseases.

To learn more, visit mda.org/care/mda-care-centers.

National Ataxia Foundation (NAF) is dedicated to improving the lives of people living with ataxia through support, education, and research. At ataxia.org, there are free publications on FA management topics, such as the importance of exercise and the purpose of an ataxia diet.

To learn more, visit ataxia.org.

This list is provided for informational purposes only and may not be a fully inclusive or updated list of all such networks. Biogen also makes no representations or warranties with respect to any of these organizations.

Importance of Healthy Eating

A registered dietitian nutritionist can counsel patients on how food choices might promote health and better disease management.

The recommended diet for most patients with ataxia is similar to what you might expect for general healthy eating. Please be mindful that between 8% and 32% of patients with FA also have diabetes and these patients will require extra dietary guidance not covered in this section.[4]

Goals[15]

The goal of diet guidelines for ataxia is not to offer a cure for FA but rather to:

- Reduce the severity of some bothersome symptoms
- Reduce reliance on poorly tolerated or contraindicated pharmacotherapies
- Enhance the patient's perception of personal control and sense of responsibility for the management of his/her neurological condition

Benefits[15]

Some of the benefits of an ataxia diet include:

- Sound nutrition to support healthy body weight and normal bodily functions. It is important to achieve an appropriate body weight for improved movement ability and lower stress on joints
- Increased energy and less fatigue
- High fiber may add regularity to bowel movements
- Improved mood and spirit

High-fiber diet[15]

- Ataxia patients may benefit from a diet that restricts simple carbohydrates and is high in fiber. Ataxia patients may crave high-sugar foods; however, these foods may cause even more fatigue and depression than they relieve
- Certain patients may benefit from fiber supplements. Recommended dietary fiber intake is 30 to 40 grams a day; 15 grams is the norm for adults in the United States

Role of Physical Activity[15]

While healthy eating is a great start, most patients with ataxia may also benefit from regular exercise. A physical therapist on your patient's care team ensures that they are instructed on exercises tailored to delay the advancement of balance problems.

The Role of the mFARS

The primary goal of FA management is to help patients maintain their overall health and independence for as long as possible. The Modified Friedreich Ataxia Rating Scale (mFARS) is a tool to help achieve this goal. The assessment provides a clinically meaningful way to track the progressive effects of FA on your patient's physical function and to anticipate the impact on their daily living. Because of their correlation with disease progression, changes to mFARS scores over time are typically accepted as an endpoint in clinical trials for potential new FA treatments.

DOMAIN	RELATED DAILY ACTIVITIES	ASSESSMENT GOALS	WHAT THIS MEANS FOR THE PATIENT
Bulbar Function	Swallowing or speaking	Measure strength and volume of coughing and clarity of speech[16]	Reduced ability to cough brings greater risk of respiratory infection.[17] Loss of speech (dysarthria) impacts communication[18] **Care considerations:** Regular vaccinations, cough-assist devices, speech therapy
Upper Limb Coordination	Brushing teeth, typing, pointing, reaching, turning a doorknob	Measure motor abilities related to tremors, fine motor coordination, and steadiness of hands and arms[16]	Self-dressing and feeding may be affected, as well as handwriting and typing/texting.[19] **Care considerations:** Voice-based virtual assistant technology, occupational and/or physical therapy
Lower Limb Coordination	Pressing foot pedals when driving	Measure coordination of legs and feet[16]	Lower limb coordination closely relates to upright stability and is a strong indicator of disease progression.[20] **Care considerations:** Mobility aids (e.g., cane, walker, wheelchair); occupational and/or physical therapy
Upright Stability	Walking, getting out of a chair, climbing the stairs, or showering	Measure loss of ambulation and impaired ability to coordinate voluntary movements[16]	The course of disease for each patient is most evident in this domain. Over time, these scores help predict loss of function.[20] **Care considerations:** Mobility aids (e.g., cane, walker, wheelchair), occupational and/or physical therapy

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Managing Your FA Patients

This brochure is designed as a resource for neurologists managing FA patients.

What's inside:

A closer look at common symptoms of FA

Detailing the multidisciplinary care team

Getting connected to the FA community

Discussing nutrition and exercise with patients

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