FRIEDREICH’S ATAXIA BACKGROUNDER AND IMPORTANT CONSIDERATIONS

Important information that may help you manage your patients with FA

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

### Reflexes, muscle tone, and sensory loss
- 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
- 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
A closer look at the 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.
- 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.
- Heart failure and arrhythmias (supraventricular in origin) are the most commonly reported causes of death.

**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.
- 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.
- 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.
- 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.

**Diabetes mellitus/Hyperglycemia**
- 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.
- 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 bolus viscosity of liquids.

**Muscle weakness and wasting**
- Weakness occurs later in the course of the disease and is more prominent in the lower limbs compared to the upper limbs.
- Many patients preserve upper limb strength even when wheelchair-bound. 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.
A closer look at the common symptoms of FA (cont’d)

### Ophthalmic features
- 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.
  - However, on occasion sudden bilateral loss of vision has been observed, mimicking Leber’s hereditary optic atrophy.

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

**Progression and mortality**
- The mean duration from age at disease onset to age at wheelchair-bound is 15.5 years, on average occurring at an age of 25 years.
- 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.
- The largest retrospective study of mortality in FA looked included 61 individuals who had died.
  - 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.

Taken as a whole, these symptoms define FA. The table on the next page outlines the major clinical and genetic features that distinguish FA from other ataxias.
Clinical and genetic features\textsuperscript{1,2,7-12}

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

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

*Inherited in an autosomal dominant pattern.

APTX, aprataxin; ATM, ataxia-telangiectasia mutated; FXN, frataxin; GAA, glucosidase alpha, acid; PMP22, peripheral myelin protein 22; SACS, sacsin; SETX, senataxin.
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 counselor13
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 to 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. He or she can screen for FA complications, including cardiovascular issues, diabetes, and scoliosis.

Cardiologist13
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 and 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.

Endocrinologist13
The endocrinologist screens for glucose intolerance to establish a baseline in all patients with FA. He or she 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.

Pulmonologist13,14
Pulmonologists can provide treatment options to help keep FA 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 surgeon13
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:
- Physiatrists
- Podiatrists
- Speech therapists
- Neurologists
- Nutritionists
- Palliative care teams
- Social workers

Learn more about managing patients with FA
Consensus clinical management guidelines for Friedreich’s 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.
Importance of healthy eating

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.

- Ataxia patients may benefit from a diet that restricts simple carbohydrates and that 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 30-40 grams a day; 15 grams is the norm for adults in the United States.

Role of physical activity

While healthy eating is a great start, patients who include regular exercise in their routine may achieve optimal results. Include a physical therapist in your patient’s care team to ensure that they are instructed on exercises specifically tailored to delay the advancement of balance problems.

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 an organization 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 an organization 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)** The NAF is an organization 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**.
Eating well is an important part of maintaining overall health. Below is a list of micronutrient considerations that may help patients sustain the healthy initiative. Be mindful that micronutrient intake varies from person to person. This table is designed for adults with ataxia.

<table>
<thead>
<tr>
<th>MICRONUTRIENT</th>
<th>DOSAGE</th>
<th>CONSIDERATIONS/RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₁₂</td>
<td>100-400 mcg/day</td>
<td>Vitamin B₁₂ malabsorption and vitamin B₁₂ deficiency are more common in older adults</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>500-1000 mg/day</td>
<td>Some people find sodium ascorbate and calcium ascorbate less irritating to the gastrointestinal tract than ascorbic acid</td>
</tr>
<tr>
<td>Vitamin D₃</td>
<td>2000 IU/day (50 mcg)</td>
<td>Vitamin D is required for optimal calcium absorption. Obesity tends to reduce bioavailability of vitamin D. Aging also tends to reduce the capacity to synthesize vitamin D. Staying indoors or the regular use of sunscreen blocks vitamin D synthesis</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>200 IU/day</td>
<td>Total sources should not exceed 400 IU/day</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Women: 90 mcg/day</td>
<td>Adequate intake (AI) of vitamin K is essential in maintaining bone health</td>
</tr>
<tr>
<td></td>
<td>Men: 120 mcg/day</td>
<td></td>
</tr>
<tr>
<td>Coenzyme Q₁₀</td>
<td>100-200 mg/day</td>
<td>Coenzyme Q₁₀ is fat-soluble and is best absorbed with fats in a meal. Women who are pregnant should not take coenzyme Q₁₀</td>
</tr>
<tr>
<td>Magnesium (Mg)</td>
<td>100 mg/day</td>
<td>The metabolism of carbohydrates and fats to produce energy in the body requires numerous Mg-dependent chemical reactions. Mg may also be helpful for muscle cramps. Mg is best absorbed in aspartate or glutamate amino acid chelated form or alternatively in glutamate or lactate salts form. Mg oxide is less well absorbed</td>
</tr>
<tr>
<td>Omega fatty acids</td>
<td>2000 mg/day</td>
<td>Omega-3 (ALA, EPA, and DHA), omega-6 (GLA, linoleic acid), omega-9 fatty acids. These fatty acids require adequate vitamin E</td>
</tr>
<tr>
<td>Glucosamine sulfate only. Not glucosamine HCl or with chondroitin sulfate</td>
<td>1500 mg/day for relief of arthritis pain only in some patients</td>
<td>Three months of treatment is a sufficient period for the evaluation of efficacy; if there is no clinically significant decrease in osteoarthritic pain by this time, the supplements should be discontinued. There is no evidence that glucosamine sulfate prevents osteoarthritis in healthy persons or in persons with knee pain but normal radiographs. Avoid if allergic to shellfish</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Eat fresh vegetables and fruits daily</td>
<td>Flavonoids may provide some neuroprotective benefits by helping to reduce inflammation in the body. Resveratrol in red wine also helps with inflammation</td>
</tr>
</tbody>
</table>

ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; HCl, hydrochloride.
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
Multidisciplinary care team
Get connected to the FA community
Discussing nutrition and exercise with patients

References: