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Friedreich's Ataxia – Evaluation and Rehabilitation Management

Description

Friedreich's Ataxia (FA) is a progressive neuromuscular disorder with symptoms that include muscle weakness, ataxia, and loss of balance and coordination. The disease is commonly associated with a cardiomyopathy that may range in severity from mild to lethal. Cognition is not affected in FA. Onset of symptoms in FA typically occurs between the ages of 10 to 15 years old. Earlier disease onset is typically associated with a more severe clinical course.

Etiology

FA is caused by a repeating mutation in the frataxin gene located on chromosome 9. The protein product frataxin regulates the levels of iron inside mitochondria. The most commonly occurring mutation in the frataxin gene is a trinucleotide repeat expansion. The gene normally contains anywhere from five to 30 GAA repeats. In people with FA, the gene can contain hundreds to thousands of GAA repeats. Longer repeat expansions are associated with earlier disease onset and faster, more severe progression.

Epidemiology

FA is the most common of a group of related disorders called hereditary ataxias, affecting about one in 50,000 people.

Pathogenesis

The current prevailing theory holds that frataxin acts like a storage depot for iron, releasing it only when it is required by the cell. In the absence of frataxin, free iron accumulates in mitochondria producing oxidative stress that ultimately leads to damage and impaired cellular respiration. This widespread mitochondrial damage explains why FA is a multisystem disorder, affecting cells of the peripheral and central nervous system as well as the heart and endocrine systems.

Risk Factors

FA is inherited in an autosomal recessive pattern. Thus it takes two defective copies of the frataxin gene to cause FA, with one copy inherited from each parent, neither of whom would have FA.

In the United States, the carrier rate is approximately 1 in 100. The disease is known to be more common in some ethnic groups though. The carrier rate is as high as one in 70 people of Cajun (Acadian) ancestry in North America.

In more than 95 percent of people with FA, both copies of the frataxin gene contain expanded repeats. In the other 5% there is just one copy of the expanded frataxin gene where as the other copy contains a single point mutation (single-letter change).

In FA carriers, the frataxin gene may contain either a repeat expansion or a point mutation. Rarely there is a permutation, a number of expanded repeats occurring just below the disease-causing range. Premutations may or may not further expand into the disease-causing range in a given ova or sperm. This complicates the ability to definitively assess risk of transmission for carriers.

As with all autosomal recessive diseases, generally speaking, a child with a biological sibling affected by FA has a 25 percent chance of inheriting the disease.

Clinical Features

Natural History

FA is associated with significant ataxia which usually affects the lower extremities first. Early symptoms are typically tripping, stumbling, an unsteady gait or impaired athletic performance. Coordination and balance will progressively decline over time, along with weakness and fatigue in skeletal muscles, again typically first in the legs. Most patients with FA will become wheelchair dependent within five to 15 years after disease onset.

Patients with FA will also have dysarthria, producing a typically “ballistic” speech pattern. Word production is typically slow with an irregular pattern. This problem is entirely caused by incoordination and weakness of the tongue and other facial muscles. There is no impairment of intellect or language skills in FA. Patients with FA may also develop dysphagia and are at higher risk for aspiration.

FA also affects the spinal cord and the peripheral sensory nerves. The associated sensory neuropathy will further impair coordination through loss of proprioception. FA also affects cerebellar function, with impairment of motor planning and coordination of movement.

In the absence of a severe cardiomyopathy or restrictive breathing problems, life span can be normal or near normal.

Diagnosis

The disease is initially diagnosed on the basis of clinical presentation, and family history, if present.

Differential diagnosis

- FA can appear phenotypically similar to other forms of hereditary spinocerebellar ataxia (HSCA): HSCAs are a diverse group of autosomal recessive, neurodegenerative disorders. Phenotypes may include predominantly cerebellar ataxia or may also be associated with sensorimotor neuropathy, ophthalmological disturbances, focal motor seizures, cognitive dysfunction, and congenital skeletal malformations
- Familial Spastic Paraparesis (FSP)
- Cerebral Palsy
- brain or spinal cord tumors
- stroke
- central nervous system demyelinating diseases (i.e. multiple sclerosis)

History

a thorough history and careful assessment of your personal and family history.

Exam

- loss of reflexes is an early and universal feature of FA
- ataxia in all four limbs and trunk
- impaired finger to nose, heel to shin testing
- impaired balance and gait

Testing

- Electrodiagnostic testing (EDx) will be done, including nerve conduction testing and needle myography (EMG). Sensory nerve action potentials (SNAPs) will be typically absent or of reduced amplitude in people with FA.
- Magnetic resonance imaging (MRI) might be performed to look for any pathophysiological changes in the brain or cerebellum.

- White blood cells will be used to analyze DNA for genetic testing.

Pitfalls

- Although recent studies describe a rare variant of FA not linked to the frataxin gene, tests for frataxin mutations are highly reliable and can be used to confirm or exclude a diagnosis of FA in almost all cases. The tests also can be used prenatally and to determine carrier status
- Severity of ataxia does not predict cardiomyopathy
- Cardiac symptoms may be “silent” initially

Treatment

Medical

- Nonsteroidal anti-inflammatory medications for muscle and joint pain
- Consider Narcotic Analgesics for more severe pain
- Idebenone (a short-chain coenzyme Q10 analogue) dose at 5-20mg/kg/day – may help with cardiac function and muscle performance
- Angiotensin converting enzyme (ACE) inhibitors to reduce cardiac afterload if cardiomyopathy present; other agents include digoxin and anti-arrhythmics

Rehabilitation Therapies

- Goals include increased walking distance, decreased falls, improved gait stability, more normal gait speed, step length and cadence; increased independence in activities of daily living (ADLs).
- Physical therapy for gait training, muscle balance, core stabilization programs; wheelchair evaluation and training; instruction on use of assistive devices – canes, walkers, etc
- Occupational therapy for assistive device evaluation and for home program of sensory integration and neuromuscular coordination exercises
- Speech language pathology for linguistic and oropharyngeal exercises; augmentative communication devices

Surgical

- Spinal Fusion for progressive neuromuscular scoliosis
- Surgical correction of joint contractures if causing a functional or positional problem
- Surgical correction of structural foot abnormalities

Consults

- Neurological or orthopedic-spine surgery
- Cardiology for evaluation and treatment of cardiomyopathy

Suggested Readings

- Pandolfo M. Friedreich ataxia. *Arch Neurol* 2008; 65(10):1296-303.
- Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. *Lancet Neurol* 2007; 6(3):245-57.