Friedreich ataxia

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Abstract
Friedreich ataxia is transmitted as an autosomal recessive trait. Onset often occurs in childhood or adolescence, but also sometimes in adulthood. In France prevalence is estimated to 1 in 50,000 and males and females are equally affected. Friedreich ataxia is characterized by difficulties to coordinate movements, associated with neurological signs (dysarthria, loss of reflexes, decrease of deep sensation, pes cavus and scoliosis), cardiomyopathy and sometimes diabetes mellitus. Ataxia is progressive, with an inability to walk alone 10 to 20 years after the disease onset. The causative gene has been identified in 1996 and codes for frataxin. Diagnosis can be made by genetic testing. The disease is due to a frataxin deficiency, which affects the mitochondrial function and the energetic metabolism of the cell. New treatments restoring mitochondrial functions are currently being assessed. Management should address the neurological and cardiological disorders as well as diabetes mellitus. Functional rehabilitation plays a predominant role in the management of the disease.

Key-words
Friedreich ataxia, neurodegenerative disease, *frataxin*

Definition / Diagnosis criteria

Friedreich ataxia is the most common inherited ataxia. The mean age at onset is approximately 15 years and 80% of the cases occur before age 20. However, later onset may occur up to the seventh decade. Diagnosis is suspected on the basis of a slowly progressive ataxia that is inherited as an autosomal recessive trait.

Differential diagnosis

A Friedreich ataxia-like syndrome, AVED, is produced with selective vitamin E deficiency. AVED is much more frequent in North Africa than in Europe. Its diagnosis is based on the measurement of the plasma levels of vitamin E. The causative gene has been localized to chromosome 8. This differential diagnosis is crucial because AVED is one of the rare neurodegenerative diseases whose evolution can be reduced or stopped using vitamin E oral supplementation.

Incidence

The incidence of Friedreich ataxia has been estimated to 1 in 50, 000 in Europe.

Clinical description

The usual presenting symptoms include pes cavus and unsteady gait. The disease is

characterized by a wide spectrum of manifestations:
- *Progressive neurological manifestations* consisting of a cerebellar syndrome, first static and then kinetic (dysmetria, balance disorders) with dysarthria, deep sensory loss (areflexia), a pyramidal syndrome (bilateral Babinski's sign) and a sensory axonal neuropathy. Other neurological signs (hearing impairment, optic atrophy) may also manifest. A pyramidal syndrome with retained or even brisk reflexes is commonly found in late onset forms and in forms associated with a mutation in the the *frataxin* gene, and may lead to spasticity;
-*Osteoarticular manifestations* including bilateral symmetric pes cavus, kyphoscoliosis in more than 75% of cases.
-*Visceral and endocrine manifestations*: hypertrophic cardiomyopathy often occurs 4 or 5 years after the first neurological signs, but may precede them in some early-onset forms of Friedreich ataxia. Its incidence increases as the disease progresses. Subaortic stenosis may sometimes occur. Diabetes mellitus is found in 10 to 20% of patients.
The neurological manifestations result mainly from the degeneration of the dorsal root ganglia, posterior funiculus of the spinal cord and spinocerebellar tracts. The degeneration is slowly progressive. Loss of ambulation occurs approximately 15 years after the disease onset and patients may die from cardiopulmonary complications, often between the age of 40 and 50 years.

Management including treatment
Recent studies have demonstrated that coenzyme Q or derivatives (Idebenone) improve anomalies of mitochondrial respiratory chain in muscles. Idebenone has been proved to be efficient in the treatment of cardiomyopathy in patients with Friedreich ataxia, but its effects on neurological signs seem limited and are under investigation. Owing to the absence of severe side effects of Ibedebone in Friedreich ataxia, this treatment is now proposed to all patients at a dose of 5 to 7.5 mg/kg/day. Marketing approval has been requested and awaits approval, but in the meantime temporary authorization for the drug prescription is available in France.
Symptomatic treatments that aim to avoid the disease's complications, notably the cardiac involvements such as cardiac insufficiency and arrhythmia, and to maintain quality of life at its optimal level, must also be emphasized. Management based on physical therapy, speech therapy and occupational therapy are useful with regard to making full use of the patient's existing muscular capacities. Alleviating scoliosis is essential to maintain sitting position and respiratory function. Diabetes mellitus requires specific treatment. Contractures can be reduced with some pharmacological treatments. Serotonin precursors may improve cerebellar ataxia. Use of some antibiotics (penicillin, phenicols, aminoglycosides, sulfonamides, nitrofurantoins) and curarizing drugs is not recommended. Self-help devices, such as electric uprighting wheelchairs and communication aids, are efficient and useful for maintaining a relative autonomy. Animal models mimicking neurological and/or cardiac features of the disease have been generated, and might be used in screens for potential new therapies.

Etiology
Friedreich ataxia is inherited as an autosomal recessive trait. *Frataxin*, the gene responsible for the disorder, was first localized in 1988 to the chromosomal region 9q13 and later identified in 1996. A GAA trinucleotide repeat expansion in intron 1 of the *frataxin* gene is found in more than 95% of patients. This genetic anomaly results into reduced amounts of frataxin mRNA. The exact function of frataxin is yet unknown, but the protein is thought to play a role in the assembly and/or transport of mitochondrial iron-sulfur proteins involved in the respiratory chain.
The trinucleotide repeat expansion is identified by "long range polymerase chain reaction" or Southern blot assays, and point mutations are detected by sequencing of the *frataxin* gene.
The age of onset, progression to ambulation loss, occurrence of several clinical signs including cardiomyopathy and loss of tendons reflexes, are all correlated with the size of the GAA expansions. The best correlation is shown with the shortest of the two expanded GAA repeats.

Diagnostic methods
Diagnosis is clinically suspected in young patients with progressive ataxia and dysarthria, loss of tendon reflexes and Babinski's sign. Electromyogram (EMG) reveals sensory axonal neuropathy. About 80% of patients have abnormal electrocardiogram or cardiac echography, due to hypertrophic cardiomyopathy. Diagnosis is based on DNA analysis revealing the characteristic GAA expansion, present on both alleles in most cases. The identification of the *frataxin* gene enabled inclusion of additional forms within the clinical spectrum of Friedreich ataxia, such as adult forms with an age of onset up to the seventh decade, forms with tendon reflexes preserved in the inferior limbs, and even forms associated with a predominant pyramidal syndrome.

Genetic counseling
Sibs of an affected individual are at 25% risk of inheriting the disorder. Due to its autosomal recessive transmission mode, the disease rarely manifests in two successive generations. If an individual is detected as an homo- or hetero-zygous carrier of mutations, his partner may be tested for heterozygosity. However, given the low frequency of heterozygous carriers (about 1/100), the risk of transmitting the disease to the offspring is relatively low.

Prenatal diagnosis
Prenatal testing is available for couples at risk who wish to have a child.

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