Friedreich ataxia in a family from Mali, West Africa

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Abstract

Friedreich ataxia is the most common inherited ataxia in the world, but yet to be reported in black African. We report the first genetically confirmed case in a West African family. Studying genetic diseases in populations with diverse backgrounds may give new insights into their pathophysiology for future therapeutic targets.

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Abstract

Friedreich ataxia is the most common inherited ataxia, affecting approximately 1/50,000 individuals in the Caucasian population, but yet to be reported in black African. We report here the first genetically confirmed case in a West African family.

A 17-year-old boy of seven siblings from a consanguineous marriage presented with hand tremor and slurred speech at age 11. Parents noticed progressive walking difficulty, skeletal deformities and muscle wasting but no cognitive impairment. Later, he presented with frequent falls, and was wheelchair-bound at age 16. Neurological examination found muscle weakness and atrophy worse in lower limbs, loss of vibration and joint sense, bilateral plantar extensor, brisk reflexes throughout, bilateral *pes cavus* and scoliosis. No cardiologic abnormalities were found, and blood glucose was normal. The presentation was consistent with Friedreich ataxia, and testing of the frataxin (*FXN)* gene showed an abnormal GAA trinucleotide expansion in both alleles (999 and 766), confirming the diagnosis of FRDA.

This is the first genetically confirmed Friedreich ataxia in West Africa, expanding the genetic epidemiology of this disease. Studying genetic diseases in populations with diverse backgrounds may give new insights into their pathophysiology for future therapeutic targets.

Keywords: Friedreich ataxia, *FXN* gene, genetic epidemiology, Mali, West-Africa.

Key clinical message:

Friedreich ataxia is the most common inherited ataxia in the world, but yet to be reported in black African. We report the first genetically confirmed case in a West African family. Studying genetic diseases in populations with diverse backgrounds may give new insights into their pathophysiology for future therapeutic targets.

Introduction

Friedreich ataxia is an autosomal recessive cerebellar ataxia due to a progressive degeneration of corticospinal and spinocerebellar tracts and posterior columns of spinal cord. It is the most common inherited ataxia in the world with a prevalence of 1/50,000 people. However, most cases were described in populations with Caucasian ancestry (Emily et al., 2019).

Clinically, the disease is characterized by progressive gait and limb ataxia, dysarthria, loss of vibration and proprioceptive sense, and pyramidal involvement with upgoing toes (Alper et al., 2003). Cardiomyopathy, diabetes, scoliosis and *pes cavus* are common associated systemic symptoms. MRI shows spinal cord atrophy. The disease is caused by a triplet (GAA) expansion within the first intron of the frataxin (*FXN)* gene located on chromosome 9q13 (Campuzano et al., 1996). Normal alleles have only a small number of GAA trinucleotide repeats (usually 8-33), whereas abnormal expanded alleles contain more than 90 repeats. Despite the high consanguinity rate in some West African ethnic groups, no genetically confirmed case has been reported in that region. Here we report the first genetically confirmed West African family with Friedreich ataxia caused by mutations in the*FXN* gene.

Material and Methods

Patient was seen under a research protocol approved by the institutional ethical committee of Faculté de Médecine et d'Odonto-stomatologie (FMOS), Mali. The patient was examined by a multidisciplinary team including neurologist, ophthalmologist, cardiologist and ENT specialist after giving an informed consent.

Brain MRI, nerve conduction study, and blood chemistries including vitamins B12 and E, blood glucose and blood cell counts were performed to consolidate our diagnosis and to exclude other ataxia causes. DNA was extracted from peripheral blood in the patient for genetic testing. Genetic testing was done by Athena Diagnostics in Marlborough, Massachusetts, USA.

Direct testing for the repeat expansion mutation in the *FXN* gene was performed by PCR amplification of the repeat region followed by high-resolution electrophoresis to determine the number of tandem repeats in each allele. Southern blot analysis was used, as necessary, to confirm homozygosity of normal alleles and to verify the number of repeats in highly expanded alleles. Southern blot analysis is performed using *Bsi* HKA restriction digestion of genomic DNA and hybridization with a gene specific probe. This methodology is greater than 99% accurate for the detection of repeat expansion mutations.

Results

A 17-year-old boy from a consanguineous Tuareg family (Figure 1A) was seen for walking difficulty. His past medical history was consistent with normal pregnancy and delivery, and no developmental delay. He is the second child of a sibship of seven, and presented symptoms at age 11 starting with hand tremor and slurred speech. Then, parents noticed progressive walking difficulty followed by frequent falls few months later, and skeletal deformities were noticed around age 14. These symptoms worsened gradually leading the patient to being wheel-chair bound at age 16.

Clinical examination found dysarthria with very few words, spasticity with brisk and diffuse reflexes, hypertonia with scissor legs, loss of vibration and joint sense, and bilateral extensor plantar responses. In addition, he had scoliosis, lumbar kyphosis and *pes cavus* (Figure 1B & C). Cardiologic, ophthalmologic and ENT examination revealed no abnormalities. Brain MRI showed cerebellar atrophy (Figure 1D) while nerve conduction study revealed axonal sensory polyneuropathy. Blood chemistries including blood glucose and cell counts were normal, but platelet and vitamin B12 levels were high. These features are consistent with Friedreich ataxia, and the testing of the *FXN* gene associated with this disease identified GAA expansions in the first intron of the gene in both alleles. The first allele had 999 GAA expansion while the second had 766. This haplotype was not previously reported. Clinical and laboratory findings are summarized in Table 1.

Discussion

Friedreich ataxia is the most common cerebellar ataxias in the world and mostly reported in populations with Caucasian ancestry. Only few sub-Saharan African families with Friedreich ataxia are reported in the literature and none of them had black African ancestry (Smith et al., 2016). To our knowledge, mutation in *FXN* has not been previously identified in West Africa.

The present study is the first clinical and genetic description of FRDA in a Malian patient of Tuareg origin, an ethnic group residing between Mali and Algeria. Although cases have been reported in Algeria and other Maghrebin countries, it is not clear if these included patients with Tuareg origin.

The patient presented here had classical clinical features of FRDA with hand tremor and slurred speech as presenting symptoms and longer GAA repeats as compared to the average.

It is well known that there is an inverse correlation between the size of the allele and the age at onset and the severity of the disease. The age of onset (11 years) in this study is close to the average (15 years), however, the progression of the disease was faster than reported. In fact, the lapsed time between the first symptom and wheelchair use by the patient was five years while the average time reported in the literature is 10 years. In addition, skeletal deformities appeared earlier than seen in other populations.

Although, two thirds of patients with FRDA present hypertrophic cardiomyopathy, we did not find any cardiologic features during our investigations. This might suggest the high variability in the clinical presentation or due to the youngest age of the patient as symptoms related to cardiomyopathy usually occur in the later stage of the disease (Dutka et al., 1999). A regular follow-up could detect early cardiologic involvement.

Despite the fact that diabetes mellitus occurs in up to 30% individuals affected by Friedreich ataxia, the fasting blood sugar was normal in the patient we present here.

The neuroimaging is often normal in the early stages of FRDA, but in advanced stages atrophy of the cervical spinal cord and cerebellum may be observed. However, the patient's brain MRI showed moderate cerebellar atrophy after only three years of disease progression.

Beside the relative longer length of GAA repeats in both alleles than reported elsewhere, these differences in the disease course could be stochastic or due to the lower quality of care compared to more developed countries or other genetic modifiers.

Nevertheless, large cohorts of patients with different ethnic and geographical backgrounds may be needed for genotype-phenotype correlation studies which could shed light into these hypotheses.

In conclusion, we report the first genetically-confirmed FRDA case in a West African family, expanding the genetic epidemiology of this disease. As genetic testing becomes available to African populations, future studies may uncover other FRDA cases and improve our understanding in the phenotypic variability and the role of the *FXN* gene in the function of the nervous systems. In addition, whole genome sequencing of cohorts in diverse populations may identify other disease-modifying variants that could be used as therapeutic targets.

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Author contribution:

Author 1: conception and design of the study, data interpretation, drafting of the manuscript, final approval of the version to be submitted, submission of the manuscript, agreed to be accountable for all aspects of the work.

Author 2: data interpretation, critical revising of the manuscript, final approval of the version to be submitted, agreed to be accountable for all aspects of the work.

Author 3: clinical data interpretation, critical revising of the manuscript, final approval of the version to be submitted, agreed to be accountable for all aspects of the work.

Author 4: conception and design of the study, data interpretation, critical revising of the manuscript, final approval of the version to be submitted, agreed to be accountable for all aspects of the work.

Author 5: clinical data interpretation, critical revising of the manuscript, final approval of the version to be submitted, agreed to be accountable for all aspects of the work.

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