

Friedreich Ataxia: Clinical Report of an Uncommon Point Mutation (R165C)

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Abstract

Introduction: Friedreich ataxia (FRDA) is the most common hereditary ataxia now. It is inherited as an autosomal recessive disease. Most of the patients are homozygotes, with an expansion of a GAA triplet in both alleles of the first intron of the frataxin gene (FXN, 9q13) (95-98% of the patients). The rest of the patients are heterozygotes with an expansion in only one allele and a point mutation in the other. These cases are more difficult to diagnose due to the low prevalence and the needed of enlarge molecular tests.

Case Report: An ambulant 42-year-old man was referred to our hospital due to gait instability that had started 7 years ago. A clinical examination showed gait ataxia, areflexia, decrease vibration sense, scoliosis, and pes cavus.

Results and Discussion: Laboratory tests, neuroimaging and neurophysiologic studies had been done since then without relevant findings. Somatosensory evoked potentials were also done and described a sensitive axonal neuropathy with an affection of the posterior columns of the spinal cord. Due findings of 300-350 repetitions of GAA in one allele and the point mutation R165C in the other that confirmed the diagnosis.

Conclusion: This case report highlights that, although most patients of Friedreich ataxia are usually homozygotes, there are a small number of patients that are heterozygotes and can have different phenotypes being important to identify them to give genetic counselling and detect new complications that suppose a risk for their lives.

Keywords: Friedreich's ataxia; Heterozygotes; Point mutation; R165C

Introduction

Friedreich ataxia (FRDA) is the most common hereditary ataxia and it is inherited as an autosomal recessive disease. Most of the patients are homozygotes with an expansion of GAA triplet in both alleles of the first intron of the FRDA gene (FXN, 9q13) but the rest are heterozygotes with an expansion in one allele and a point mutation in the other (2%-5%) [1,2]. There have been described missense, nonsense and splicing mutations and although the two last mutations can produce severe manifestations, missense mutations can be less sharp, with milder and atypical clinical phenotype. It has also been reported some exonic deletions, but its frequency is extremely unusual [3]. Apart from that, clinical expressions are related with the number of GAA repetitions and an inverse relation with the age of onset has been observed. Size of expansion is variable and can be between 67 to 1700 repeats (normal in humans is 7-40 repeats) and this supposes a reduction of frataxin protein due to the lack of expression of the FRDA gene [1,4].

This protein is related with the mitochondrial iron metabolism and its dysfunction produces an increase of oxygen free radicals that causes intracellular damage. Frataxin is hardly expressed in the spinal cord, cerebellum and heart so it can explain the typical clinical manifestation. It causes an affection of nervous system, skeletal and foot deformity, optic disk pallor, cerebellar dysarthria, ataxia and other diseases like diabetes and cardiomyopathy [1-3]. Most of these patients have a reduced life expectancy and it is mainly related with cardiac problems. Yet, there is not a curative treatment and all the management is focus on looking out and treats the symptomatic manifestations. Considering that Friedreich ataxia is a genetic disease is necessary to give them genetic counseling [1]. We describe a clinical case of a heterozygote patient with a missense mutation (R165C) with unusual clinical phenotype.

Case Report

An ambulant 42-year-old man was referred to our hospital due to

gait instability. His past medical history was unremarkable, although he reported some clumsiness in his childhood that did not prevent practice sports. There was not consanguinity in his family. The patient did not have any treatment. Symptoms onset were at 36 years old with gait disturbances and he went to a private center where the neurological examination only described pes cavus and areflexia. He was studied with a magnetic resonance imaging (MRI) and electrophysiological studies that did not show abnormalities. Two years later he came back due to worsening of the gait and new MRI was done showing a small lumbar disk protrusion that did not justify the clinic. It was also made a new electrophysiological study that showed a decrease of amplitude in right peroneal nerve and he was also studied by otorhinolaryngology that described a global imbalance with not vestibular relation. When he was 42 years old he came to our hospital because of the persistence of gait disturbances. We reviewed all the studies and the clinical reports that had been done previously. The new neurological examination revealed gait ataxia, areflexia, decrease vibration sense, scoliosis, and pes cavus. The systemic exploration was normal. Analysis with ions (including copper and ceruloplasmin), blood count, vitamins, hormones, proteins, serology, and autoimmunity study were normal. Somatosensory evoked potentials were also done and described a sensitive axonal neuropathy with an affection of the posterior columns of the spinal cord. Taking the evolution of the patient into account and the results of the studies that had been done, several diagnoses were considered thinking in a genetic neuropathy with compromise of the posterior columns.

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We enlarged the analysis with a study of long chain fatty acids that were normal and a genetic study of the gen TTR and FDRA. There was no mutation in TTR but in FDRA was found an expansion of 300-350 repetitions of GAA in one allele. After these findings and because of the clinical exploration was compatible with Friedreich ataxia, a new test genetic was solicited looking for a point mutation that was finally detected in the other allele (C493 C>G; p (Arg165Cys)). The expansion detected and this point mutation in heterozygosis confirmed the diagnosis of Friedreich ataxia. A transthoracic echocardiogram (TTE) and an ECG was performed without abnormalities and genetic counseling was given.

Discussion

Although most patients with Friedreich ataxia are homozygotes, there are a small percentage that are heterozygotes. It has been described forty-four different mutations in FXN gen, including point mutations, insertion and/or deletion. Missense mutations usually affect protein structure and/or function [1,5]. It is also known that the number of repetitions of GAA reduce frataxin expression and due to this, large repetitions cause an early onset [1,5]. In our patient was found a small expansion of 300-350 repetitions of GAA in one allele that might have contributed to the late onset. Our patient was diagnosed when he was 42 years old. He was heterozygote and had a missense mutation (R165C) in which there was a substitution from arginine to cysteine in this position. This mutation is not located in the domain of the carboxy-terminal frataxin and this produces a less severe phenotype, as Palau's article describes [1]. Researching in literature, there are not so many cases described with this kind of mutation. Forrest et al. found a woman with a relatively mild presentation in her middle age (27-years-old) without cardiac affection. We ignore her expansion of GAA [6].

In the study of Galea et al. is said that this mutation has a mild to moderate effect in the protein stability, but it causes an important reduction in its union with other molecules [7]. The discovery of the mutations in the FRDA has permitted a diagnosis of this disease in patients with an atypical clinical and a later onset than traditional forms [8]. In the literature there are two main forms of late-onset atypical presentation: late-onset FRDA (LOFA) (onset between 25-39 years) and very late-onset FRDA (VLOFA) (> 40 years). In this forms gait and limb ataxia are present and dysarthria appears later during the disease. Other manifestations as scoliosis, pes cavus, cardiomyopathy and diabetes are less frequent in atypical patients although abnormal electrocardiogram can appear [9].

Conclusion

Despite of been inherited as a recessive disease, Friedreich ataxia

(FRDA) there is not such clinical homogeneity as in other recessive disorders and due to the atypical presentation of our patient, another sensitives neuropathies were taken into account and a differential diagnosis were made with them (hereditary sensory and autonomic neuropathy, Fabry disease, Familial amyloidotic polyneuropathy, Adrenomyeloneuropathy etc.) but the normality of the probes that have been done and the lack of another symptoms related with these diseases caused that Friedreich ataxia was suspected. With this case we make relevance that not all patients have an early onset, or a severe phenotype and a good neurologic exploration is important to recognize them. Once the diagnosis is made, it is necessary to follow them in consults paying attention to heart problems and giving them genetic counseling.

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