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Very Late-Onset Friedreich Ataxia with Laryngeal Dystonia

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Key Words
Autosomal recessive neurodegenerative disorder · Friedreich ataxia · Laryngeal dystonia

Abstract
Friedreich ataxia (FRDA) is an autosomal recessive neurodegenerative disorder characterized by progressive gait and limb ataxia, cerebellar, pyramidal and dorsal column involvement, visual defects, scoliosis, pes cavus and cardiomyopathy. It is caused by a homozygous guanine-adenine-adenine (GAA) trinucleotide repeat expansion in intron 1 of the frataxin gene *(FXN)* on chromosome 9q13-q21.1. Onset is usually in the first or second decade of life; however, late-onset cases of Freidreich ataxia (LOFA), after the age of 25 years, and very late-onset cases of Freidreich ataxia (VLOFA), after the age of 40 years, have been reported. VLOFA is quite rare and usually presents a milder progression of the disease. We report the case of a 64-year-old woman affected with VLOFA whose first symptoms (balance and gait disturbances) occurred at the age of 44 years. At the age of 62 years, she started complaining of a slowly progressive dysphonia showing the clinical aspects of laryngeal dystonia. Molecular analysis showed a 210- and 230-trinucleotide GAA repeat expansion in the two alleles of the *FXN* gene. Laryngeal dystonia has been reported only in very few cases of ataxia syndrome and never before in FRDA patients. It may represent a rare clinical manifestation of VLOFA thus confirming the high variability of the clinical spectrum of FRDA.

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Introduction

Friedreich ataxia (FRDA) is an inherited autosomal recessive disease usually linked to a homozygous guanine-adenine-adenine (GAA) trinucleotide repeat expansion in the first intron of the frataxin gene *(FXN)* on chromosome 9q13-q21.1. Only 2–4% of patients are compound heterozygotes for the GAA expansion on one allele and a deletion or point mutation on the other. There is a direct correlation between the size of the GAA expansion and the phenotype: large GAA repeats are associated with earlier age of onset and a more rapid progression of the disease [1]. The effect of mutation is a reduced synthesis of frataxin, a nuclear encoded mitochondrial protein that plays a role in iron homeostasis [1].

Although FRDA is typically a clinically homogeneous disease that affects young individuals with onset around puberty, some rare cases of late-onset (LOFA) and very late-onset Freidreich ataxia (VLOFA) have been reported as well as heterogeneous clinical presentations [2–4]. The variability in the age of onset and the presence of 'atypical' clinical features can make it difficult to rapidly achieve a correct diagnosis.

We herein expand the disease phenotype by reporting the case of a woman with VLOFA associated with laryngeal dystonia.

Case Report

A 64-year-old woman complained of slowly progressive imbalance in standing and gait and lower limb stiffness since the age of 44 years. Her symptoms progressed slowly over the years, and after 20 years she had lost most of her autonomy in the basic activities of daily living. At the age of 62 years, she started complaining of a slowly progressive dysphonia, resulting in a whispering voice. ENT examination diagnosed an abductor-type laryngeal dystonia which had no manifest causes, and which was not responsive to L-Dopa, botulinum toxin, and logotherapy.

The patient's past medical history revealed erosive *Helicobacter pylori*-positive gastritis, irritable bowel syndrome, migraine without aura and cervical and lumbar arthrosis. Her family history was unremarkable. At the age of 64 years, neurological examination showed a spastic-ataxic gait worsened by eye closing, dysarthria with slurred speech, mild limb dysmetria, decreased deep tendon reflexes, extensor plantar responses and loss of vibratory and proprioceptive sensation.

MRI of the brain (fig. 1), MRI spectroscopy and SPECT were unremarkable. Evoked motor and sensory potentials showed slowed central conduction velocity. Nerve conduction studies and electromyography were normal. The videofluoroscopic swallowing study was normal.

Echocardiography showed normal cardiac function with normal thickness of the septal and left ventricular walls. Pulmonary dynamic functional indices and lung volumes were within normal limits, while respiratory muscle strength showed a marked reduction both in inspiration and expiration, indicating involvement of both the diaphragm and skeletal respiratory muscles. Antigangliosides, anti-MAG and onconeural antibodies were negative. Genetic analyses for spinocerebellar ataxias types 1, 2, 3, 6, 15/16, 17 and dystonia type 4 were negative. Molecular analysis showed a 210- and 230-trinucleotide GAA repeat expansion in the two alleles of the *FXN* gene.

Discussion

FRDA is usually a disease starting at young age, causing progressive disability and confinement to a wheelchair after 10–15 years from onset. Diagnostic clinical criteria include: (1) age of onset before the end of puberty, (2) progressive ataxia of gait and limbs, (3) absent knee and ankle jerks, (4) dysarthria, (5) pyramidal weakness in lower limbs, (6) axonal damage on electroneurography, and (7) large fiber sensory loss on pathological examination [5]. Hypertrophic cardiomyopathy, increased risk of diabetes mellitus and skeletal abnormalities (i.e., kyphoscoliosis and pes cavus) are also common features [5].

The identification of the disease gene has allowed large screenings in ataxic patients and has resulted in a widening of the spectrum of clinical presentations. About 25% of patients harboring the *FXN* molecular defect do not fulfill the above-mentioned clinical criteria and may show 'atypical' features including retained tendon reflexes, tabetic phenotype, unusually slow progression and delayed age of onset [4].

LOFA and VLOFA are defined by onset after the age of 25 and 40 years, respectively [2, 3]. Usually, late-onset forms of FRDA are associated with a milder disease with slower progression and a smaller number of GAA repeats (<500 GAA). VLOFA is very unusual and is caused by <300 GAA repeats in at least one of the expanded alleles. It is likely that other genetic and environmental factors as well as levels of residual frataxin in affected tissues may modulate the clinical features, severity and rate of progression of FRDA [1, 3].

Our case is one of the rare cases of VLOFA having <300 GAA repeats in both alleles, and represents the first description of abductor laryngeal dystonia in FRDA. Laryngeal dystonia, also known as spasmodic dysphonia, is a focal action-induced form of dystonia that affects the vocal cords and is characterized by involuntary movements of one or more muscles of the larynx during speech [6]. It can be a primary disease (sporadic or idiopathic) or a secondary condition (trauma, infections, drugs, underlying neuromuscular disorders). The most frequent adductor type causes a tight, strangled-sounding voice, often with abrupt starting and stopping. The abductor type causes a breathy, whispering voice that sometimes progresses to aphonia. A mixed-type and an adductor laryngeal breathing dystonia causing persistent inspiratory stridor and paroxysmal cough usually with normal voice have also been reported [6].

Laryngeal dystonia has already been described in only a few cases of SCA20, familial dystonia and multiple system atrophy [7–9]. In some other ataxia syndromes (i.e., SCA1, SCA3), a vocal cord abductor paralysis has been reported [10].

The exclusion of acquired conditions and the progressive course of dysphonia in our patient suggest that laryngeal dystonia may represent a rare clinical manifestation of FRDA. Our report confirms the high variability of the clinical spectrum in FRDA. Presence of laryngeal dystonia in a patient with an ataxic syndrome should lead physicians to consider FRDA in the differential diagnosis.

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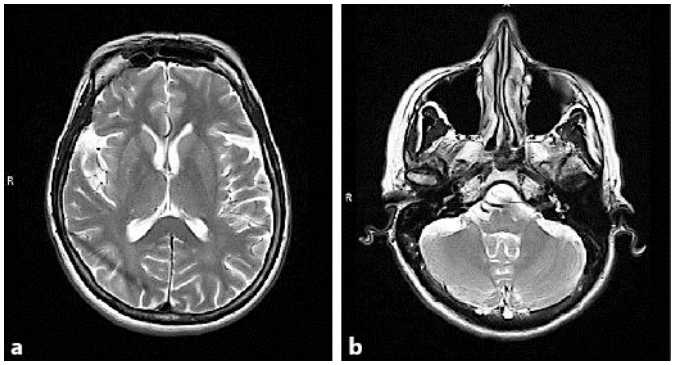

Fig. 1. MRI of the brain. No significant cortical (**a**) or cerebellar atrophy (**b**) is present. The brain stem is normal.