Blindness and Deafness – an Extreme Phenotype in Friedreich Ataxia

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Abstract

Introduction

Friedreich ataxia is the most frequent hereditary ataxia worldwide. Subclinical visual and auditory involvement has been recognized in these patients, with co-occurrence of severe blindness and deafness being rare.

Case Report

We describe a patient, homozygous for a 873 GAA expansion in the *FXN* gene, whose first symptoms appeared by the age of 8. With 22 years-old he developed sensorineural deafness, and with 26 visual impairment. Deafness had a progressive course over eleven years, until a stage of extreme severity which hindered communication. Visual acuity had a catastrophic deterioration, with blindness three years after visual impairment was first noticed. Audiograms documented progressive sensorineural deafness, most striking for low frequencies. Visual evoked potentials disclosed bilaterally increased P100 latency. He passed away at the age of 41 years old, at a stage of extreme disability, blind and deaf, in addition to the complete phenotype of a patient with Friedreich ataxia of more than 30 years duration

Discussion

Severe vision loss and extreme deafness has been described in very few patients with Friedreich ataxia. Long duration, severe disease and large expanded alleles may account for such an extreme phenotype; nonetheless, the role of factors as modifying genes warrants further investigation in this subset of patients.

Introduction

Friedreich ataxia (FRDA) is the most frequent hereditary ataxia worldwide. The underlying genetic mechanism is, in the majority of patients, an unstable, pathological GAA expansion in *FXN* gene leading to decreased expression of frataxin, a ubiquitous mitochondrial protein [1]. First symptoms usually appear around puberty, and cardinal neurological features include cerebellar ataxia, sensory loss, pyramidal signs and absent reflexes in lower limbs [2]. Atypical phenotypes, with retained reflexes, late or very late onset have been thoroughly characterized for the last years [3]. The most frequent non-cerebellar symptoms encompass cardiac repolarization abnormalities, cardiomyopathy, scoliosis and urinary system disorders [2, 4]. Optic and auditory involvement may also be present in FRDA, but less frequently than the previous ones [2, 4, 5].

Here we highlight the co-occurrence of blindness and deafness as part of an extreme FRDA phenotype.

Patients And Methods

The patient was part of a prospective study on hereditary cerebellar ataxias approved by the Institutional Ethics Committee. From 2016 until 2019 he was evaluated through a structured protocol, comprising age-at-onset of the various neurological symptoms/ signs, the Scale for the Assessment and Rating of Ataxia (SARA) and the Inventory of Non-Ataxia signs (INAS). Every six months a questionnaire on new neurological symptoms and the INAS was applied, as well as a complete neurological exam, comprising SARA. The missing clinical information was obtained through a detailed review of medical records and video files. Brain MRI was performed in 1.5 tesla scanner. DNA was collected from peripheral blood of patient and parents, and stored at CGPP-IBMC, i3S.

Case Report

This was a male patient, homozygous for a 873 GAA expansion in the *FXN* gene (Fig. 1a), who presented gait instability by age 8 years. Dysarthria and upper limbs dysmetria emerged subsequently; 4 years after disease onset he was wheelchair-bound. Scoliosis was diagnosed at age 16, and cardiomyopathy detected one year later. When 22 years-old he complained of bilateral hypoacusia, progressing to severe deafness over 11 years. By age 26, visual impairment was noticed and rapidly deteriorated: visual acuity decreased to 0.4 in just one year, and further decreased to light perception in the following two years. At that time, fundoscopic exam showed marked pallor of the optic discs, with sharp edges and normal retina. There was no history of exposure to drugs or toxins that could affect vision or hearing. Diabetes was diagnosed in his early thirties. By the age of 40 he presented scandid dysarthria, blindness, decreased amplitude of horizontal saccades, severe deafness impairing communication, tetraparesis predominantly affecting the lower limbs, absent deep tendon reflexes, absent position sense in the halluces, and truncal and finger-to-nose ataxia (video). Even though a neuropsychological assessment could not be performed, there was no evidence of cognitive deterioration. He passed away with 41 years, after severe pneumonia. By the time visual and hearing impairment were first noticed, a thorough investigation was conducted: haemogram, chemistry, serology and immunology studies were normal. Genetic variants associated with Leber hereditary optic neuropathy (LHON) were excluded. Visual evoked potentials disclosed bilaterally increased latency (right eye: 144 milliseconds, left eye: 148 milliseconds) and decreased amplitudes of P100. Audiograms documented progressive sensorineural deafness, most striking for low frequencies (Fig. 1b-c). On brain MRI, there was cerebellar, pons and medulla atrophy, with optic nerves exhibiting normal thickness and signal (Fig. 1d-f).

Discussion

The first description of optic atrophy in FRDA was made by Sjögren, in 1940, in 12% of his patients [2]. Later, Harding identified optic atrophy in 30% of her cases: 5.2% with severely and 13% with mildly reduced visual acuity, the remaining being asymptomatic [2]. Deafness was present in 7.8%, ranging from severe (0.9%) to mild (5.2%) [2]. Highly significant clustering of optic atrophy (with visual acuity < 6/12) with diabetes and deafness was identified, with Harding hypothesizing that modifying genes would be the most likely explanation for this association [2].

Across the years, a few studies have demonstrated that subclinical involvement of visual and auditory systems is more frequent than blindness or deafness [5–7]. Reduced visual acuity has been identified in 3.1–13% [4, 6, 8], and increased latency of visual evoked potentials in 34–70% [5, 6, 9]. All 26 patients studied by Fortuna et al had thinning of the retinal nerve fibre layer on optical coherence tomography, in spite of only five having reduced visual acuity [5]. Posterior visual pathways impairment may also be present, with significantly higher apparent diffusion coefficients on diffusion-weighted MRI of the optic radiations [5]. When considering auditory function, hearing loss measured by audiogram has been reported in 10–13% [4, 6, 8], with abnormal conduction in central pathways being more frequent [6–8, 10]. Patients with normal or near-normal sound detection may present abnormal cochlear nerve or auditory brainstem responses [7, 10]. Impaired speech-understanding at levels of everyday background noise has also been reported, developing as soon as early-school years [7, 10].

Severe vision loss resembling LHON was described in very few patients, all with severe disease, long duration and large expanded alleles [5, 11]. Most were compound heterozygotes, and in one it was associated with diabetes [5, 11]. The patient here reported had a catastrophic and rapidly progressive optic neuropathy. Auditory impairment had a more protracted course, with progressively elevated hearing levels in audiograms, reaching a stage of critical deafness. Notwithstanding the relative frequency of visual and auditory impairment in FRDA, such profound deficits are not common. Homozygosity for a large expansion and long disease duration could partly account for such a severe phenotype.

Underlying pathophysiological mechanisms are incompletely understood. Current evidence suggests that decreased levels of frataxin leads to mitochondrial dysfunction and increased susceptibility to oxidative stress of the nervous system, including visual and auditory pathways [5].

With this report we wish to further contribute to the characterization of optic and auditory involvement in FRDA. Improved healthcare services with longer survival of early-onset patients will probably increase the frequency of these devastating manifestations. Nonetheless, the role of factors as modifying genes warrants further investigation in this subset of patients with severe blindness or deafness.

Declarations

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Conflict of interest/ Disclosure

Joana Damásio has received a research grant from Centro Hospitalar Universitário do Porto and has received a speaking fee from Zambon. Ana Sardoeira, Maria Araújo, Isabel Carvalho, Jorge Sequeiros and José Barros have nothing to disclose.

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Compliance with ethical standards

This work is part of a project that has been reviewed and approved by the institutional review board from Centro Hospitalar Universitário do Porto.

Consent to participate and consent to publish

Permission for the publication of this article and associated video was obtained from the patient and his parents, via written informed consent, in compliance with laws regarding patient authorization relating to the use or disclosure of protected health information.

Authors contributions

JD – Conception and execution of the project. Writing of the first draft.

AS – Organization and execution of the project. Review and critique.

MA – Execution of the project. Review and critique.

IC – Execution of the project. Review and critique.

JS – Conception of the project. Review and critique.

JB – Conception of the project. Review and critique.

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Figures

Figure 1

a) Long-range polymerase chain reaction of intron 1 of FXN gene, showing the homozygous 873 GAA expansion (patient); three controls (heterozygote, sample with two normal alleles and blank – B) are shown. GeneRuler 1 kb DNA Ladder is flanking the samples for allele size determination. b-c) audiograms documenting progressive sensorineural deafness (b: 2003, c: 2011). d) (T2): optic nerves exhibiting normal thickness and signal. e (T1) and f (T2)) atrophy of vermis and cerebellar hemispheres.

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