Friedreich's Ataxia and Auditory Processing Disorder

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Friedreich's ataxia (ATX-FXN) was described by Nikolaus Friedreich's in 1863 and is the most common autosomal recessive ataxia worldwide [1–3]. The estimated carrier frequency in the general population is 1/60 to 1/90 and prevalence of the disease has been estimated in a variety of Western European populations between 1:20,000 and 1:125,000 [1–3]. In the large majority of cases (95%), the disease is caused by a pathological homozygous repeat expansion of a trinucleotide repeat (GAA: usually between 100 and 1300 repeats) in intron 1 of the X25 frataxin (FXN) gene on chromosome 9q13 [1–3]. The severity of the phenotype correlates with the size of the GAA expansion. The mutation causes a defect of transcription and lack of FXN, a small mitochondrial protein, resulting in a complex neurological presentation. Although the exact function of FXN is still a matter of discussion, there is general agreement that the protein is involved in cellular iron homeostasis and that its deficiency results in multiple enzyme deficits, mitochondrial dysfunction, and oxidative damage [1, 2].

The “classical” phenotype of ATX-FXN is characterized by progressive gait and limb ataxia, dysarthria, loss of lower limb reflexes with deep sensory loss, Babinski's sign, eye movement abnormalities, particularly square-wave jerks, hypermetric saccades and saccadic pursuit, optic atrophy, and the presence of extra-neurological signs including scoliosis, pes cavus, foot deformities, hypertrophic cardiomyopathy, and diabetes mellitus [1–3]. At least 35% patients present with

atypical clinical picture (variants), including LOFA (late-onset cerebellar ataxia) and VLOFA (very late-onset cerebellar ataxia). Delayed-onset forms are characterized by a less severe phenotype, a slower progression, retained reflexes, or even hyperreflexia and spasticity. Rare cases have been described presenting with chorea, dystonia, and myoclonus [1–4]. In addition to a better identification of the various phenotypic presentations, neuroimaging studies have expanded our understanding of the repercussions of the disease on the central nervous system [1, 2]. Magnetic resonance imaging (MRI) was used to diagnose ATX-FXN before gene testing was available, and thinning of the cervical spinal cord was a consistent observation [2, 5, 6]. Atrophy of the cerebellum and brainstem was more variable, but in structural exams performed in recent years, the images have clearly revealed atrophy of the dentate nuclei and degeneration of the superior cerebellar peduncles [2, 5, 6]. Diffusion tensor imaging (DTI) and tract-based spatial statistics (TBSS) also clearly demonstrate the extensive cerebral and cerebellar involvement in ATX-FXN [5]. A multimodal MRI-based study has investigated the anatomical substrates involved in the early stages of ATX-FXN and suggests that structural damage begins in pediatric patients in the spinal cord and inferior cerebellar peduncle, as well the red nucleus, and progresses to widespread cerebral areas in adulthood [6]. These findings contribute to our understanding of the different clinical phenotypes of the disease.

Several studies have demonstrated impaired vestibular functions in ATX-FXN, detected by caloric tests, rotatory tests, and head impulse tests (HIT) [7, 8]. Histopathological studies have revealed gliosis in the vestibular nucleus [9] and abnormalities of the vestibular nerve [10]. Up to 10% of patients complain of hearing loss [8]. Defective central auditory processing is common in ATX-FXN and can promote difficulties in verbal communication [11, 12]. Conventional tests such as brainstem auditory evoked potentials (BAEPs) show increased latencies or dys-synchronization in waves I, III, and V, and in delays the inter-peak intervals I–III, I–V, and III–V [12]. Wave V may be undetectable. These findings confirm

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alterations in the integrity of the brainstem auditory pathways. Pure tone audiometry and acoustic immittance measures may be impaired also. Damage to the cochlear nerve without involvement to inner ear structures has been reported [10], with spiral ganglion degeneration [13]. The auditory neuropathy of ATX-FXN might be related to a mechanism of fast energetic failure [14]. Auditory perception is commonly abnormal in ATX-FXN if investigated correctly. What we tend to think as normal hearing (the pure tone audiogram) is limited to normal hearing sensitivity. Holistically evaluating hearing abilities in any individual requires testing for hearing sensitivity as well as for auditory processing abilities [15]. While there are studies showing deficits in auditory processing in ATX-FXN, the systematic implementation of an auditory processing battery that provides a good view to hearing is rarely the case. This issue of *Cerebellum* includes an innovative paper entitled “Auditory phenotypic variability in Friedreich’s ataxia patients” by Prof Bamiou’s team linking auditory processing disorder (APD) with genotype as well as cognition [16]. Implications include (i) early identification and appropriate management of APD may have a positive effect on cognition by ameliorating deficits that have a negative effect on the quality of life, and (ii) auditory deprivation should not be solely thought as an abnormal audiogram as hearing encompasses many facets. The link between auditory deprivation (in this case of the form of APD) and cognition has long-term outcomes and should not be thought as a cross-sectional one [17, 18]. Thus, it is of outmost importance to longitudinally evaluate patients with ATX-FXN, document the cognitive deficits when identifying APD at an early stage, and provide appropriate management for these challenging patients. Could this improve patients’ quality of life? This remains to be confirmed. Furthermore, the issue of a possible use of these findings as a biomarker for longitudinal or therapeutic studies remains open and requires novel studies.

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