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Letter to the Editor

Late-onset hummingbird sign in a woman with fragile X premutation

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1. Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a disease caused by a CGG repeat expansion of 55 to 200 replicates in the *FMR1* gene located on the X-chromosome. FXTAS usually presents with tremor and cerebellar ataxia, but the phenotypic spectrum is broad and include parkinsonism, peripheral neuropathy, autonomic problems, cognitive deficit, and psychiatric disturbances. The typical recognized feature of FXTAS in brain magnetic resonance imaging (MRI) is white matter lesions in the middle cerebellar peduncle (MCP). Other typical findings include hyperintensity in the splenium of the corpus callosum, in the pons, insula and periventricular regions, in addition to cerebellar and cortical atrophy [1].

The hummingbird sign, also known as the penguin sign, refers to the midbrain atrophy with no pontine atrophy described in progressive supranuclear palsy (PSP) patients. This sign has been useful in differentiating PSP from other parkinsonian syndromes and is best seen in midsagittal image which reveals a flat and concave-contoured midbrain [2]. This sign has already been reported in FXTAS [3].

Herein we report an 82-year-old female patient who developed a slowly-progressive gait impairment during the last two years. Brain MRI revealed the hummingbird sign without the MCP sign. There was a positive family history for FXTAS and patient tested positive for the FMR1 gene.

2. Case report

An 82-year-old woman presented with a two-year history of a slowly-progressive gait impairment and postural instability, which caused frequent falls. Her 60-year-old son had similar symptoms since age 54 (Video 1 – Segment 1) and the brain MRI revealed bilateral MCP sign and hyperintensity in the corpus callosum (Fig. 1). Her son's *FMR1* gene analysis revealed a premutation (100 CGG repeats), confirming the diagnosis of FXTAS. Patient's nephews had the classic presentation

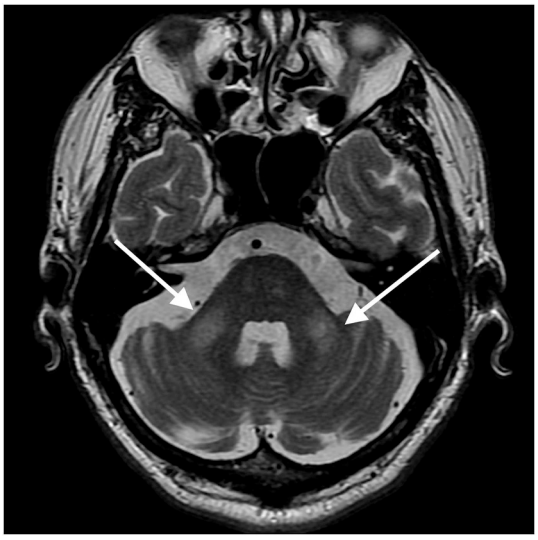

Fig. 1. (Patient's son brain MRI): axial T2-sequenced imaging showing bilateral abnormal high signal intensity in the middle cerebellar peduncles (white arrows)

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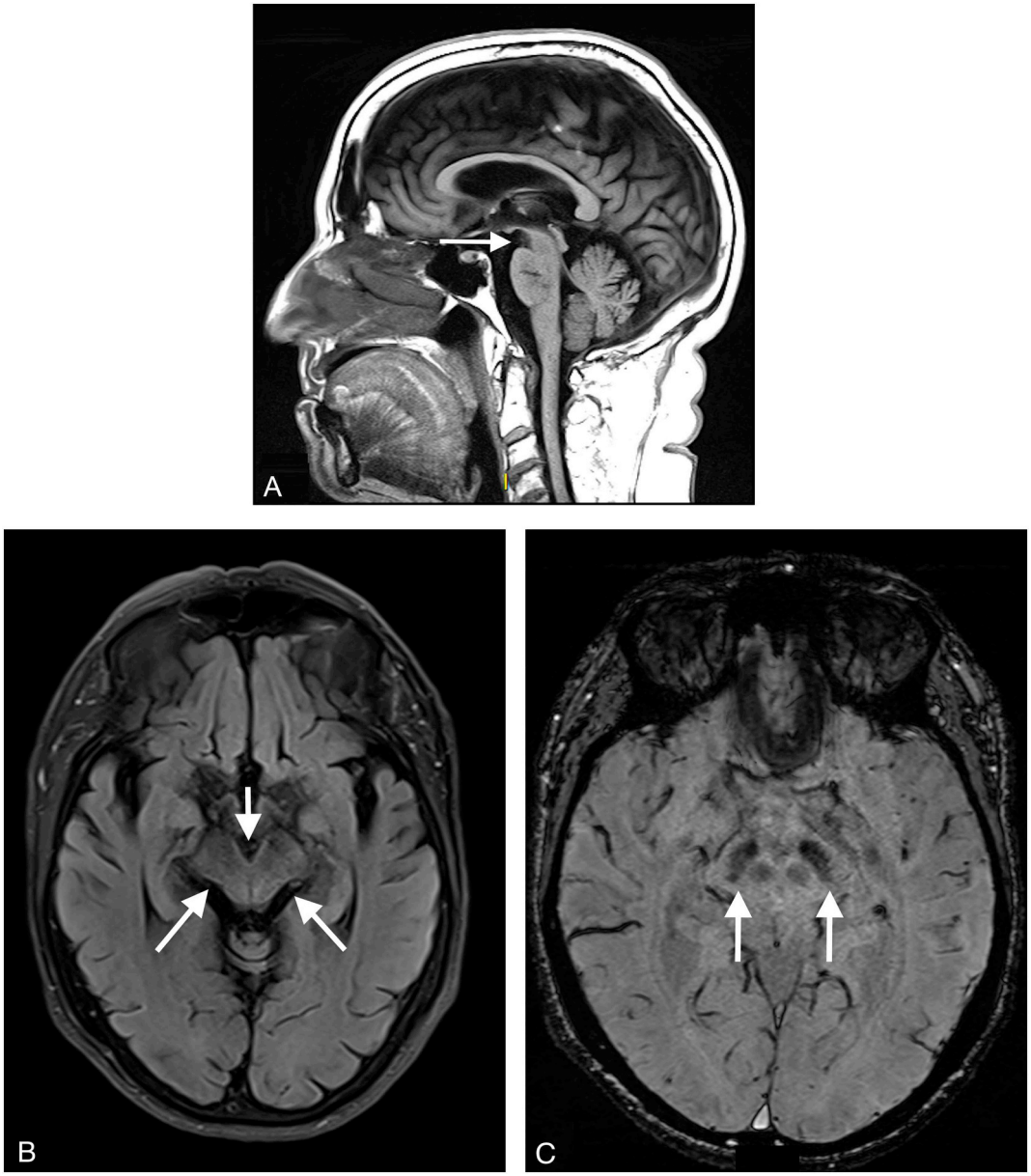

Fig. 2. A–C (Patient's brain MRI): A: Sagittal T1-weighted sequence revealing mild mesencephalic atrophy resembling the hummingbird sign (white arrow); B: Axial Flair-weighted sequence showing mesencephalic atrophy with interpeduncular fossa enlargement and postero-lateral concavity (white arrows); C: Axial susceptibility-weighted imaging showing reduced nigrossome-1 in posterior aspect of substantia nigra probably related to nigro-estriatal pathway degeneration. Her middle cerebellar peduncle (not shown here) was normal.

of fragile-X mental retardation syndrome. Her previous medical history was unremarkable, without endocrine disturbances, such as primary ovarian insufficiency syndrome or hypothyroidism. Patient was unable to perform a tandem gait and had axial rigidity and prominent postural instability in neurologic examination (Video 1 – Segments 2 and 3). There were no other movement disorders, cognitive or psychiatric symptoms, and there was no supranuclear gaze palsy. Brain MRI showed the hummingbird sign (Fig. 2A and B). Axial susceptibility-weighted images showed reduced nigrossome-1 in posterior aspect of the substantia nigra, suggesting impairment in nigroestriatal pathway (Fig. 2C). *FMR1* gene analysis revealed a premutation with 75 CGG repeats. She was followed up through three years with stability of symptoms and no additional signs of PSP. Levodopa 800 mg daily resulted in no improvement.

3. Discussion

The hummingbird sign is highly specific for the diagnosis of PSP, but has been previously associated with FXTAS, but usually linked to other typical findings. Shelton et al. [3]. have shown that MCP width as well as midbrain and pons cross-sectional area were reduced in patients with FXTAS compared to both premutation carriers without FXTAS and controls. The authors suggest that FXTAS-related neurodegeneration may accelerate otherwise normal age-related decreases in midbrain and pons cross-sectional areas, with the hummingbird sign appearing in those with greater CGG repeat lengths. In a study using SPECT imaging, Scaglione et al. [4]. showed that FXTAS determines a subcortical gray matter degeneration involving the midbrain and striatum usually associated with parkinsonism. Atrophy of the midbrain with an anterior-posterior diameter smaller than 17 mm was observed in all of their patients.

The pathological hallmarks of FXTAS is the presence of eosinophilic intranuclear *FMR1* mRNA-containing inclusions in neurons and astrocytes in diffuse regions [1]. PSP presents neuropathologically with loss of substantia nigra pigment corresponding to nigrostriatal dopaminergic degeneration and microscopic findings include neuronal loss, gliosis, and neurofibrillary tangles in basal ganglia, diencephalon and brainstem. Although FXTAS and PSP might share macroscopic atrophic changes in similar areas of the brain (midbrain and striatum, for example), they do not share microscopic pathological features. However, a previous clinical and molecular study of FXTAS patients with parkinsonism [5] showed a correlation between *FMR1* mRNA and bradykinesia, suggesting an association with dopamine deficiency. This may implicate a pathophysiological mechanism that links *FMR1* mRNA toxicity to the dopamine pathway, leading to parkinsonism in FXTAS.

In conclusion, this patient had prominent axial rigidity, postural instability and brain MRI features suggestive of PSP, even in the absence of bulbar features and ophthalmoplegia. Our report brings about important issues related to the association between *FMR1* gene premutation and PSP. Firstly, women with *FMR1* gene premutation may present with very late onset of neurological symptoms and brain MRI abnormalities resembling PSP. Secondly, it is possible that this phenotype may be associated with a non-responsive dopaminergic dysfunction, since axial susceptibility-weighted images showed reduced nigrossome-1 in posterior aspect of the substantia nigra.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.06.016.

Financial disclosure

We have nothing to disclose.

Ethical statement

Full consent was obtained from the patient for the case report publication.

Declaration of Competing Interest

We have no conflict of interest.

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