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FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME

A.S. Michel, B. Claikens[1]

Key-word: Brain

Background: A 64-year-old male experiences resting and intentional tremor. The complaints aggravated progressively over the last few years and appeared first at the head and later at the upper limbs. In the end, word finding difficulties, broad-based ataxic gait and erectile dysfunction added to the symptoms. Detailed familial history reveals that 2 nephews of the patient are known to have the fragile X syndrome. Genetic analysis of the FMR1 gene shows the patient carries a pre-mutation expressing 75 repeats.

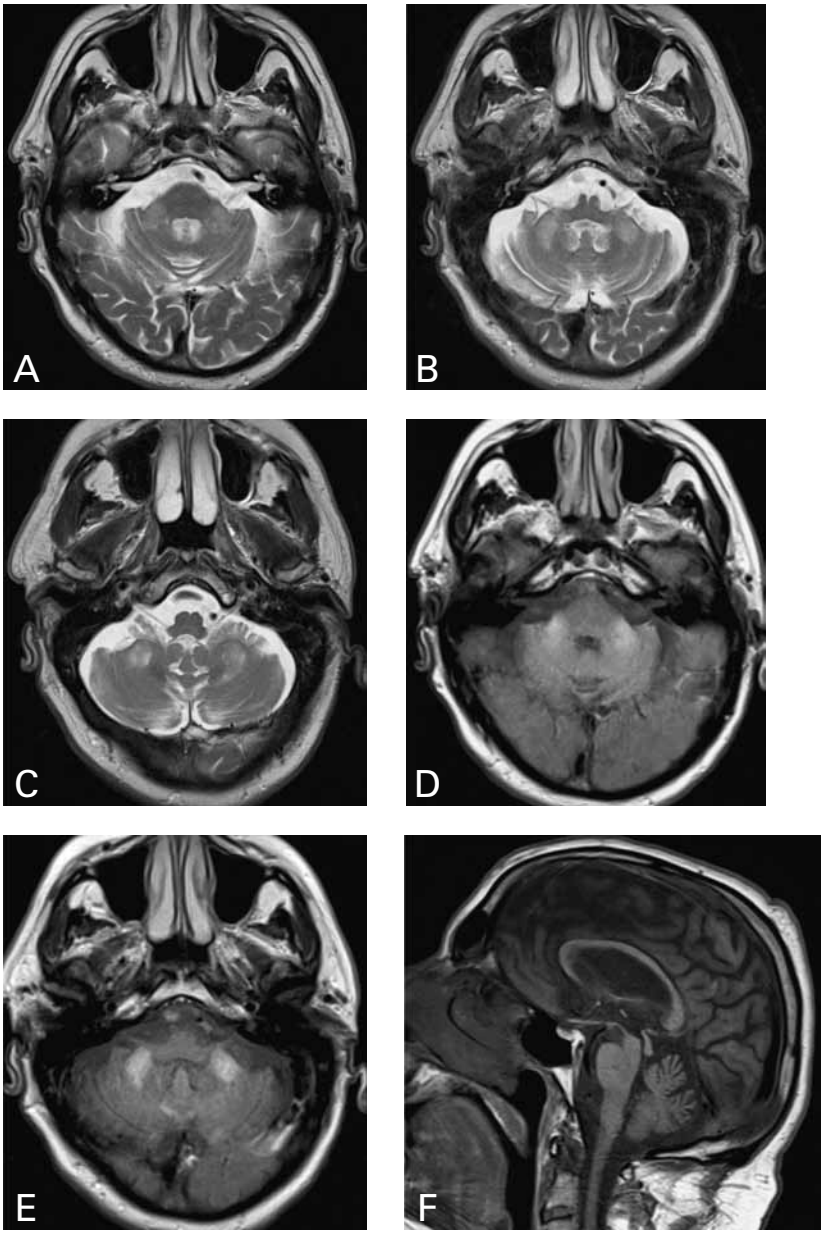

Fig. 1A | 1B
1C | 1D
1E | 1F

1. Department of Radiology, AZ Damiaan Oostende, Oostende, Belgium

Work-up

MRI of the brain (Fig. 1) consisted of axial T2-weighted images of the posterior fossa (A-C) that showed increased signal intensity in deep white matter of the cerebellar hemispheres and the middle cerebellar peduncles, while sparing the dentate nuclei of the cerebellum. Slight cerebellar volume loss is also present. Axial flair images (D,E) confirmed the involvement of the white matter inferiorly and laterally to the deep cerebellar nuclei. Sagittal midline T1-weighted image (F) demonstrated minimal atrophy of the pons with more prominent prepontine cistern. Also marked thinning of the corpus callosum is present.

Radiological diagnosis

The combination of the clinical features and the characteristic findings on MRI of the brain were suggestive of the diagnosis that was confirmed by the genetic testing: the *fragile X-associated tremor/ataxia syndrome.*

Discussion

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder occurring in male and rarely in female carriers of a premutation expansion located in the 5'-untranslated region of the fragile X mental retardation 1 (FMR1) gene. Fragile X syndrome, the most common inherited form of mental retardation, is typically caused by a repeat length greater than 200 in this FMR1 gene. The premutation consists of a trinucleotide CGG repeat length ranging from 50 to 200. Carriers of the FMR1 gene premutation are usually unaffected by the cognitive impairment associated with the full mutation. Approximately 20 to 33 percent of adult male premutation carriers display the FXTAS phenotype, and the prevalence of the premutation carrier state is as high as one in 813 males. Onset is typically at age 50-70 years and includes progressive intention tremor and/or gait ataxia. Additional clinical features of FXTAS can be parkinsonism, executive cognitive deficits, peripheral neuropathy and erectile dysfunction. Characteristic findings on magnetic resonance imaging (MRI) include, according to the age of the patient, more pronounced cerebral and cerebellar cortical volume loss, thinning of the corpus callosum and volume loss of the pons. White matter disease is almost always present and includes decreased T1 and increased T2 signal intensity in deep white matter of the cerebellar hemispheres and the middle cerebellar peduncles (MCP), while sparing the dentate nuclei of the cerebellum. The abnormal white-matter signal seen in the MCPs on MRI corresponds to spongiform changes associated with mild axonal and myelin loss. White matter disease associated with astrocytic pathology is seen on neuropathological examination, and intranuclear inclusions are present in both neurons and astrocytes in brain and spinal cord. Although the MRI presentation is not unique to FXTAS, its differential diagnoses tend to occur much less frequently: olivopontocerebellar atrophy, specific forms of autosomal dominant cerebellar ataxia, dentatorubral-pallidoluysian atrophy, multiple system atrophy, Wilson's disease and neurofibromatosis. In older men with late onset cerebellar ataxia and the described characteristic MRI findings, clinicians should strongly consider the genetic testing for the FMR1-gene mutation in order to confirm the diagnosis of FXTAS.

Bibliography

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