Fragile X-associated tremor/ataxia syndrome: cognitive presentations

Introduction

The most common genetically determined cause of intellectual disability in men is the fragile X syndrome resulting from a trinucleotide (CGG) repeat expansion in the 5' promoter region of the fragile site mental retardation 1 (FMR1) gene located on the X chromosome at Xq27.3-Xq28 (Online Mendelian Inheritance in Man [OMIM] catalogue number #300624) (Verkerk et al, 1991). Lesser numbers of CGG repeats in the FMR1 gene, between 50 to 200, are termed premutations and are associated with the fragile X-associated tremor/ataxia syndrome (OMIM#300623) (Jacquemont et al, 2007; Hagerman and Hagerman 2013; Hall et al, 2014). Identification of children with fragile X syndrome may lead to identification of parents or grandparents with fragile X-associated tremor/ataxia syndrome.

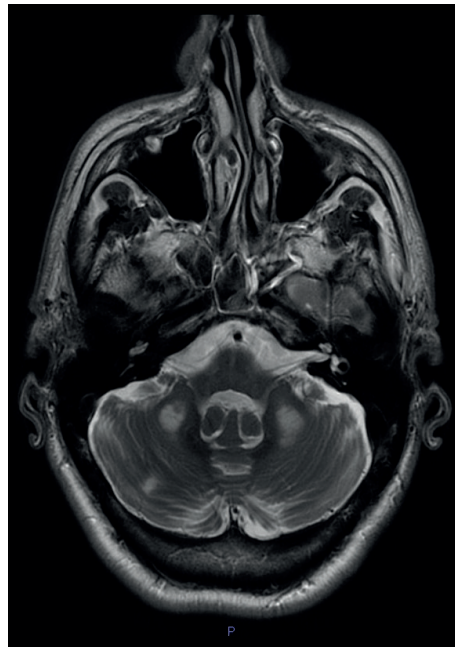
Clinically fragile X-associated tremor/ataxia syndrome is characterized by progressive cerebellar ataxia and a tremor which may have postural, action or resting components. Additional clinical features which may be seen include parkinsonism, peripheral neuropathy and autonomic features (Hall et al, 2014). These symptoms may cause misdiagnosis of fragile X-associated tremor/ataxia syndrome, for example as other tremor or ataxia syndromes (Hall et al, 2005). Magnetic resonance brain imaging in fragile X-associated tremor/ataxia syndrome typically shows high signal intensity lesions on T2-weighted images in the middle cerebellar peduncles and in white matter inferior and lateral to the deep cerebellar nuclei, with additional cerebellar and cortical atrophy (Brunberg et al, 2002).

Cognitive impairment and dementia may also be features of fragile X-associated tremor/ataxia syndrome, which has on occasion resulted in misdiagnosis of fragile X-associated tremor/ataxia syndrome as a dementia syndrome of Alzheimer or vascular type (Hall et al, 2005). This article presents two cases in which cognitive and behavioural problems were the presenting or most prominent early features of fragile X-associated tremor/ataxia syndrome, with resulting diagnostic delay.

Discussion

In addition to tremor and ataxia, fragile X-associated tremor/ataxia syndrome may also manifest cognitive symptoms. Current diagnostic criteria feature moderate to severe short-term memory deficiency and executive function deficits as minor diagnostic criteria (Hall et al, 2014). Although tremor and ataxia often precede cognitive symptoms, the phenotype of fragile X-associated tremor/ataxia syndrome is broad, extending beyond the

Figure 1. Axial T2-weighted magnetic resonance brain imaging at the level of the posterior fossa showing symmetrical bilateral high signal intensity lesions extending from the middle cerebellar peduncles ('MCP sign') into the cerebellar white matter, with cerebellar atrophy.



CASE REPORT 1

A 62-year-old man developed concerns about his memory and was referred to a local memory clinic. Neuropsychological assessment showed difficulties in attention, processing speed and executive function, but there was no memory or language deficit. No specific diagnosis was reached but follow-up for interval assessment of cognition was advised.

Six months later, the patient was referred to the neurology clinic because of intermittent tremor affecting his right (non-dominant) hand and some feelings of unsteadiness when walking (the latter had apparently been assessed in an ear, nose and throat clinic, with no cause found). He reported that his brother and sister also had hand tremors. No abnormal neurological signs were found on examination.

Because of the prior history, cognitive function was also assessed at the neurology clinic. On Mini-Addenbrooke's Cognitive Examination (MACE) he scored 24/30, dropping 4 points on verbal fluency. On the Montreal Cognitive Assessment (MoCA) he scored 25/30, with 4 points lost on attentional tests. On both MACE and MoCA there was preserved orientation, immediate and delayed memory, and visuospatial function. On the informant AD8 scale, his partner scored him 4/8 (normal <2/8).

Magnetic resonance brain imaging showed abnormal signal bilaterally in the middle cerebellar peduncles ('MCP sign') with some cerebellar atrophy (*Figure 1*).

The clinical and neuroradiological findings suggested a diagnosis of fragile X-associated tremor/ataxia syndrome. Genetic testing for the CGG expansion in the fragile site mental retardation 1 gene showed presence of the premutation (59–200 repeats), confirming the diagnosis.

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scope of the 'tremor-ataxia' nomenclature. Of note, ataxia may not be prominent even with radiological evidence of cerebellar involvement (middle cerebellar peduncle (MCP) sign, cerebellar atrophy), as in these patients.

In some patients memory and executive dysfunction may be experienced before onset of tremor and ataxia (Grigsby et al, 2008). This may explain why a previous case series found dementia to be one of the diagnostic categories for which fragile X-associated tremor/ataxia syndrome was most frequently mistaken, along with parkinsonism and stroke (Hall et al, 2005). Hence, fragile X-associated tremor/ataxia syndrome merits consideration in any male with tremor and/or ataxia disorder who also complains of cognitive decline, or with a family history of the same, or with a family history of fragile X syndrome. It was the latter which prompted correct diagnosis in case 2. The typical neuroradiological findings ('MCP sign') alerted the authors to the correct diagnosis in case 1, emphasizing the potential value of neuroimaging in establishing a diagnosis in patients with cognitive symptoms.

Although on occasion mistaken for Alzheimer's disease (Hall et al, 2005), the pattern of cognitive deficits in fragile X-associated tremor/ataxia syndrome is distinct from Alzheimer's disease, usually manifesting as a dysexecutive syndrome, with reduced processing speed, sometimes with psychiatric phenomena (mood dysregulation), as seen in case 2 (Bacalman et al, 2006).

Diagnosis of cognitive impairment as a result of fragile X-associated tremor/ataxia syndrome may have implications not only for family genetic counselling and screening, but also for treatment. The NMDA (N-methyl-D-aspartate) receptor antagonist memantine, which is licensed for the treatment of moderate Alzheimer's disease, has been shown to have effects on verbal memory and attentional processes in fragile X-associated tremor/ataxia syndrome (Yang et al, 2014, 2016), although this is not yet a licensed indication. **BJHM**

CASE REPORT 2

A 65-year-old man was referred for psychiatric assessment because of change in personality over the previous 18 months, characterized by irritability, angry outbursts, easy frustration, and some verbal and physical aggression (throwing objects). There was no prior or family history of psychiatric disorder. Although there were no specific cognitive symptoms reported by the patient or his family, he performed poorly on tests of verbal fluency and abstraction, while memory, orientation and visuospatial skills were preserved. The psychiatrist considered a diagnosis of frontotemporal dementia and arranged magnetic resonance brain imaging which was reported to show non-specific periventricular and subcortical white matter change consistent with small vessel ischaemia but no focal atrophy.

Meantime, a neurological referral had been made because of gait difficulty and sleep disturbance. The latter had features compatible with a diagnosis of rapid eye movement (REM) sleep behaviour disorder. Neurological examination found rigidity in the lower limbs. The combination of parkinsonian signs, REM sleep behaviour disorder and frontal executive type cognitive impairments prompted a provisional diagnosis of dementia with Lewy bodies, although there was no history of visual hallucinations. A trial of levodopa did not help his gait.

Diagnostic clarity subsequently came from the family history, when a grandson was diagnosed with fragile X syndrome, confirmed on DNA testing, which raised the possibility that his grandfather might have fragile X-associated tremor/ataxia syndrome. Genetic testing for the CGG expansion in the fragile site mental retardation 1 gene showed presence of the premutation (>90 repeats), confirming the diagnosis. Review of the magnetic resonance brain imaging showed unequivocal symmetrical signal change in the middle cerebellar peduncles and cerebellar atrophy.

LEARNING POINTS

- Fragile X-associated tremor/ataxia syndrome is characterized not only by tremor and ataxia but also by cognitive deficits.
- Cognitive symptoms may sometimes be the presenting feature of fragile X-associated tremor/ataxia syndrome.
- The fronto-subcortical pattern of cognitive deficit (executive dysfunction, slowed processing speed) should not be confused with Alzheimer's disease but might be mistaken for frontotemporal dementia or, when there are concurrent parkinsonian features, dementia with Lewy bodies.
- Diagnosis of fragile X-associated tremor/ataxia syndrome may have implications for other family members in terms of diagnostic or predictive genetic testing.
- Preliminary data suggest that memantine may have beneficial effects for the cognitive symptoms of fragile X-associated tremor/ataxia syndrome, but this is not currently a licensed treatment.

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