CASE REPORT

More than meets the eye: an unusual Parkinson’s disease mimic

Verónica Cabreira¹, Eva Brandão², and João Massano¹

Abstract

Introduction: Fragile X-associated tremor/ataxia syndrome (FXTAS) is a rare, X-linked adult-onset neurodegenerative disorder affecting carriers of the fragile X mental retardation 1 (FMR1) gene premutation, a 55-200 cytosine-guanine-guanine [CGG] repeat expansion in the 5’ untranslated region of the gene. Intention tremor and ataxia are usually the core features of the syndrome, while parkinsonism has also been described, but less frequently seen. FXTAS probably remains underdiagnosed, possibly mistaken for essential tremor, various degenerative ataxias, and atypical parkinsonian syndromes. Hyperintensity of the middle cerebellar peduncle (MCP) detected in T2 or FLAIR MRI, a highly specific sign of this disorder, is present in approximately 60% of men with FXTAS.

Case report: We present the unusual case of a patient with previously undiagnosed FXTAS who was referred for deep brain stimulation (DBS) surgery, as the phenotype resembled Parkinson’s disease (PD). An MRI scan requested in 2006 had revealed symmetrical T2 hyperintensity in the middle cerebellar peduncles. Genetic testing disclosed FMR1 premutation with 90 CGG repeats expansion confirming the diagnosis of FXTAS.

Discussion: This case highlights the relevance of considering FXTAS as a possible diagnosis in these cases, even if the clinical picture resembles PD. MCP hyperintensity seen on MRI should therefore trigger genetic testing and subsequent appropriate management.

Keywords: Parkinsonism, Parkinson’s disease, Fragile X-associated Tremor/Ataxia Syndrome, differential diagnosis, FMR1.

Citation: Cabreira et al. More than meets the eye: an unusual Parkinson’s disease mimic. International Journal of Clinical Neurosciences and Mental Health 2018; 5:8
DOI: https://doi.org/10.21035/ijcnmh.2018.5.8
Received: 23 Oct 2018; Accepted: 18 Nov 2018; Published: 4 Dec 2018

© 2018 Cabreira et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

¹Department of Neurology, Centro Hospitalar de São João, Porto, Portugal
²Department of Neurology, Centro Hospitalar de Entre Douro e Vouga, Santa Maria da Feira, Portugal
³Department of Clinical Neurosciences and Mental, Faculty of Medicine University of Porto, Portugal

Correspondence: João Massano
Department of Neurology, Centro Hospitalar de São João
Alameda Professor Hernani Monteiro, 4200-319 Porto, Portugal

E-mail address: jmassano@med.up.pt
Introduction

Parkinsonism can be seen in several disorders, including Parkinson’s disease (PD) and several other degenerative parkinsonian disorders. Accurate diagnosis is important, as there are important differences regarding diagnostic testing, genetic counseling, and therapy [1,2]. Fragile X-associated tremor/ataxia syndrome (FXTAS) is a rare, X-linked adult-onset neurodegenerative disorder affecting carriers of the fragile X mental retardation 1 (FMR1) gene premutation, a 55-200 cytosine-guanine-guanine [CGG] repeat expansion in the 5’ untranslated region of the gene. FXTAS differs genetically from the fragile X syndrome as the second is associated with more than 200 CGG repeats of the same gene [3,4]. FXTAS was initially described in men, typically over 55 years old, and was also recognized in women with premature ovarian failure [3]. Evidence suggests that the number of CGG repeats is a predictor of disease severity [3]. Diagnostic criteria for FXTAS were proposed in 2003 [4,5]. While intention tremor and ataxia are deemed to be the core features of the syndrome, parkinsonism, executive dysfunction, short-term memory deficiency, peripheral neuropathy and autonomic symptoms are also included in the diagnostic clinical criteria [6]. Regarding parkinsonism, as opposed to idiopathic PD, the characteristic resting tremor, cogwheel rigidity, and postural instability are less frequently seen in FXTAS [7]. The major radiological diagnostic criterion of FXTAS is symmetrical T2/FLAIR hyperintensity in the middle cerebellar peduncles (MCP sign) [4,5]. MRI findings may also include cerebral and cerebellar cortical volume loss, as well as subcortical white matter lesions. Hyperintensities in the splenium of the corpus callosum have recently been proposed as an additional radiologic diagnostic criterion for FXTAS [4,6,8]. The pathophysiological mechanism by which premutation leads to disease remains uncertain but it has been suggested that increased FMR1 mRNA levels may exert a neurotoxic gain of function effect [3], a common mechanism also occurring in other repeat expansion diseases such as several spinocerebellar ataxias. We therefore present this case as a relevant example of FXTAS misdiagnosed as PD in order to raise awareness of this possible differential diagnosis in patients whose clinical picture resembles classical PD, reinforcing the fundamental role of MRI for this diagnosis.

Case report

A 68 year-old man, initially diagnosed with PD, was referred to evaluation for deep brain stimulation surgery. The patient described progressive rest and action tremor of both hands, starting more than a decade ago. There was also a positive history of head tremor, unsteady gait and occasional falls. Levodopa had been previously initiated with reasonable symptomatic improvement. His current medication was levodopa/carbidopa/entacapone 100/25/200mg five times daily, ropinirol prolonged release 10mg qd, and amantadine 100mg bd. He was also treated for depression, deemed reactive to the motor disability, with sertraline 100mg qd, and had received prostatic surgery 6 years before due to benign hyperplasia. There was no other relevant past medical history. He had a healthy 41 year-old daughter who has a healthy 12 year-old son and a 6 year-old daughter suspected to have mild developmental delay (not examined by us); family history was otherwise unremarkable. Examination on this first visit revealed moderate predominantly right-sided bradykinesia and rigidity, hypomimia and hypophonia, postural instability, difficulty arising from a chair, slow and slightly wide-based gait without freezing, decreased arm swing predominantly on the right side, and occasional rest, slow frequency tremor of the left hand and slight postural intermediate frequency tremor of both hands. Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) motor score was 44. Neuropsychological examination revealed mild deficits of attention, processing speed, memory and executive functions. MRI scan had been requested in 2006, revealing symmetrical T2 hyperintensities in the middle cerebellar peduncles (Figure 1), raising the possibility of FXTAS. Consequently, genetic testing was then ordered, disclosing FMR1 premutation with 90 CGG repeats expansion, confirming the diagnosis. On a follow-up visit 4 months later, the neurological examination remained unchanged. Currently there is no evidence for a benefit of DBS in FXTAS, and the patient was not offered the procedure. The antiparkinsonian medication was deemed adequate, and the patient was referred back to the usual neurologist.

Figure 1. Axial FLAIR-weighted MRI, obtained in 2006. Note hyperintensities of middle cerebellar peduncles (arrows).
Discussion

FXTAS is a late-onset neurological disorder described in 2001 [8]. It probably remains underdiagnosed, possibly mistaken for essential tremor, spinocerebellar ataxias (SCAs), and atypical forms of parkinsonism [3]. Significant geographical variation exists in relation to the prevalence of the premutation in the FMR1 gene, with estimates of up to 1 in 251 males and 1 in 100 females [9]. A correct diagnosis of FXTAS is useful in order to prevent further unnecessary investigations, and to guide genetic counseling. We present the unusual case of a patient with previously undiagnosed FXTAS who was referred for deep brain stimulation surgery, as the phenotype resembled PD. In fact, some carriers of the FMR1 premutation manifest features characteristic of idiopathic PD, including improvement under dopaminergic medications and peak-dose dyskinesias [4]. Additionally, CGG triplet repeat number was found to be correlated with UPDRS-III scores, and nigrostriatal degeneration based on 123I-Ioflupane SPECT imaging was reported in FXTAS patients [4]. Evidence does not support screening PD patients for FMR1 expansions, although genetic testing in individuals with parkinsonism and a family history of developmental delay, prematurity ovarian failure, gait unsteadiness, FXTAS, fragile X syndrome or other FMR1 related diseases or possible phenotypes should be considered [7]. In 2002, hyperintensity of the MCP, detected in T2 or FLAIR MRI, was firstly documented as a distinctive feature in those with FXTAS, thus deemed a major diagnostic feature of FXTAS [8]. MCP sign is present in approximately 60% of men with FXTAS and it is a highly specific sign that should raise suspicion for this diagnosis [6,8].

We present the case of a man in his sixties with a history of tremor and parkinsonism initially diagnosed with PD. Clinicians should be aware of FXTAS as a possible diagnosis in these cases, even if the clinical picture resembles PD. MCP hyperintensity seen on MRI should trigger genetic testing and subsequent appropriate management. The existing evidence supporting DBS in FXTAS is limited [10], thus the procedure cannot currently be recommended in this population.

Abbreviations

CGG: Cytosine-guanine-guanine; FMR1: Fragile X mental retardation 1; FXTAS: Fragile X-associated tremor/ataxia syndrome; MCP: Middle cerebellar peduncles; MDS-UPDRS: Movement Disorders Society Unified Parkinson’s Disease Rating Scale; PD: Parkinson’s disease; SCA: Spinocerebellar ataxia

Competing interests

The author declares that there are no conflicts of interests.

References