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CASE REPORT

Atypical neurological symptoms associated with CGG expansions of the *FMR1* gene

Esteban Peña, Marcos Llanero

Esteban Peña, Marcos Llanero, Department of Neurology, Hospital Sanitas La Moraleja, 28050 Madrid, Spain
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Correspondence to: Esteban Peña, MD, Department of Neurology, Hospital Sanitas La Moraleja, Avenida Francisco Pi y Margall n° 81, 28050 Madrid, Spain. epenal.pex@sanitas.es
Telephone: +34-917-679100 Fax: +34-917-679346
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Abstract

More than 40 CGG expansions in the 5' noncoding region of the fragile X mental retardation 1 (*FMR1*) gene of the X chromosome give rise to several distinct clinical phenotypes, depending on the size of the expansion. First, more than 200 CGG expansions (full mutation) cause an inherited mental retardation called fragile X syndrome. Second, CGG expansions between 55 and 199 (premutation) cause a disorder called fragile X-associated tremor/ataxia syndrome (FXTAS) which typically includes intention tremor, ataxia and specific magnetic resonance imaging (MRI) findings. Indeed, it could develop parkinsonism although it usually shows features of postsynaptic parkinsonism. Finally, CGG expansions between 41 and 54 CGG (gray zone) are not consider normal but rarely develops abnormal neurological conditions. In this sense, the aim of this study is to report two atypical cases associated with CGG expansions of the *FMR1* gene. First, a FMR1 premutation alleles carrier with an unusual phenotype, such as a presynaptic parkinsonism indistinguishable from Parkinson disease (PD) and a FMR1 gray zone alleles carrier presented with neurological features, namely hand tremor, parkinsonism and ataxia, usually described in FXTAS, as well as orthostatic tremor. We conclude that, on the one hand, FMR1 premutation alleles might cause two phenotypes of parkinsonism, such as a presynaptic phenotype, indistinguishable from PD, and a postsynaptic phenotype, associated with clinical features of FXTAS. On the other hand, although FMR1 gray zone alleles carriers were believed to have no abnormal neurological conditions, our study supports that they could develop FXTAS and other neurological disorders such as orthostatic tremor which has not been reported before associated with the *FMR1* gene.

Key words: Fragile X-associated tremor/ataxia syndrome; Fragile X mental retardation; Gray zone; Parkinsonism; Orthostatic tremor

Core tip: In this study we report two atypical cases associated with CGG expansions of the fragile X mental retardation 1 (*FMR1*) gene. First, a FMR1 premutation alleles carrier presented with a parkinsonism indistinguishable from Parkinson disease. Second, a FMR1 gray zone alleles carrier presented with orthostatic tremor and neurological features associated with the fragile X-associated tremor/ataxia syndrome, such as hand tremor, parkinsonism and ataxia.

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INTRODUCTION

More than 40 CGG expansions in the 5' noncoding region of the fragile X mental retardation 1 (*FMR1*) gene

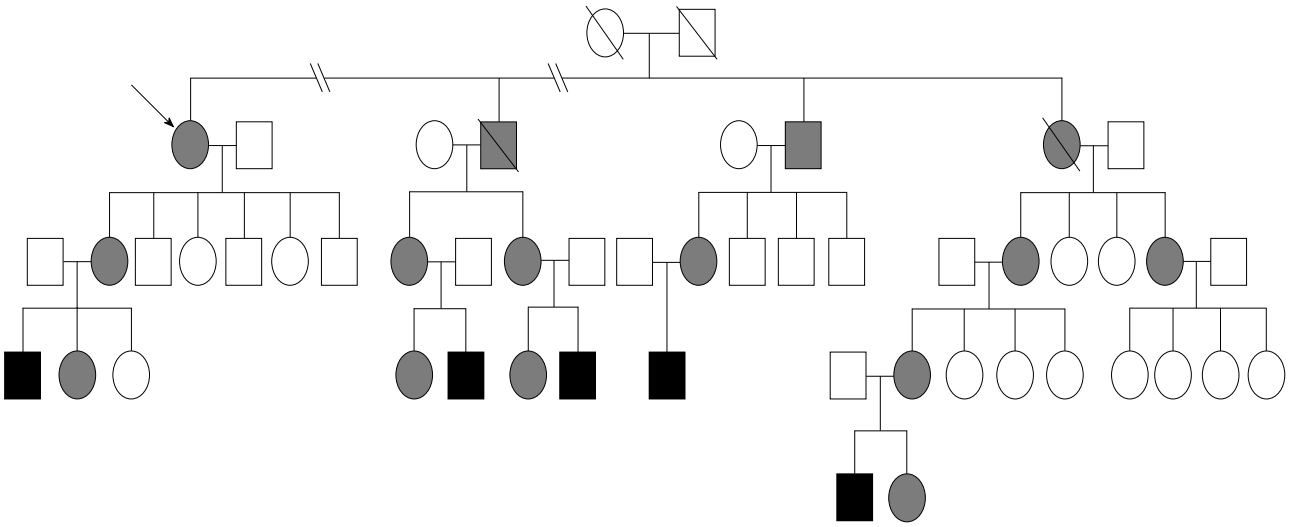

Figure 1 Pedigree structure of the patient 1 (arrow), they were 12 brothers and sisters, only those relevant are shown. Fragile X mental retardation (FMR1) CGG expanded alleles carriers are denoted as a grey filled symbol, they did not show any neurological disorder. Black filled symbols denote FMR1 CGG full mutation carriers affected by fragile X syndrome with mental retardation. Crossed symbol indicates deceased family members. Circle indicates females and square males.

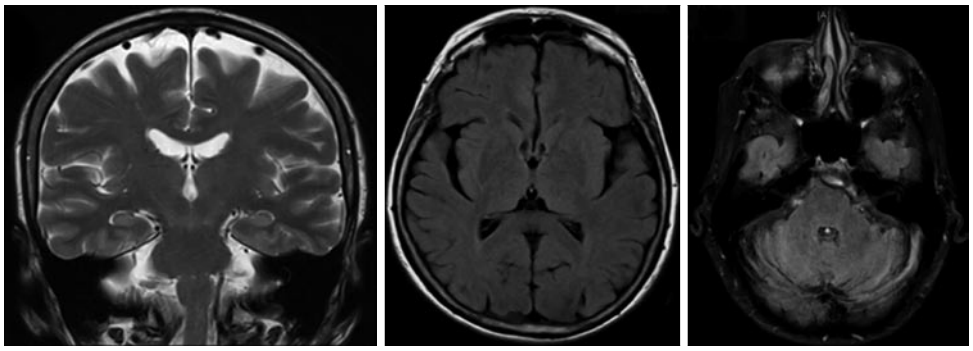

Figure 2 T2, TIR and FLAIR magnetic resonance imaging of the patient 1, it does not show abnormal findings. FLAIR: Fluid attenuated inversion recovery.

of the X chromosome give rise to several distinct clinical phenotypes, depending on the size of the expansion. First, fragile X syndrome is an inherited mental retardation caused by more than 200 CGG expansions in the *FMR1* gene (full mutation). Second, fragile X-associated tremor/ataxia syndrome (FXTAS) is a disorder described in premutation alleles carriers (55-199 CGG expansions) of the *FMR1* gene. Typically, it includes intention tremor, ataxia and specific magnetic resonance imaging (MRI) findings, although the spectrum of neurological disorders associated with the FXTAS is increasing[1-3]. Finally, an interval of CGG expansions between 41 and 54 is known as gray zone which rarely develops abnormal neurological conditions. In this sense, the aim of this study is to report two atypical cases associated with CGG expansions of the *FMR1* gene. First, a FMR1 premutation alleles carrier with an unusual phenotype, such as a parkinsonism indistinguishable from Parkinson disease (PD) and a FMR1 gray zone alleles carrier presented with neurological features, namely hand tremor, parkinsonism, ataxia and orthostatic tremor.

CASE REPORT

Case 1

A 71-year-old woman presented with a 4-year history of progressive neurological disorder with tremor, bradykinesia and gait disorder. She was FMR1 alleles carrier (expansion of 82 CGG) with family history of fragile X syndrome (Figure 1). On examination, she had severe rest and postural tremor in her right hand and slight postural tremor in her left hand, severe bradykinesia and rigidity more marked on her right side, mild lost of postural stability and freezing. There was neither intention tremor nor ataxia. Indeed, patient did not show either autonomic dysfunction or Babinski sign or gaze palsy. Finally, She had significant improvement with 520 mg of levodopa (Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale I 8 Ⅱ 17 Ⅲ ON 42 OFF 60 Ⅳ 0). These clinical findings fulfilled the United Kingdom PD Society Brain Bank clinical diagnostic criteria for idiopathic PD[4].

Blood tests and cranial MRI were normal (Figure 2).

Table 1 Neuropsychological assessment of the patient 1

Test	Subtest	Percentile
Orientation		Normal
Attention and executive functions		
D2 test of attention	Processing elements	p45
	Omissions	p25
	Concentration	p40
Digit span (WMS-III)	Forward	p50
	Backward	p50
Verbal fluency	Semantic (animals)	p75
	Semantic (names)	p90
	Phonological (FAS)	p30
Trail making test	A	p50
	B	p20
Stroop		p50
Hanoi tower	3 disk	Normal
	4 disk	Not solved[1]
Similarities (WAIS)		p50
Wisconsin card sorting test	Categories completed	4 (P > 16)
	Failure to maintain set	p51
	Errors	p30
	Perseverative responses	p30
	Perseverative errors	p30
	Conceptual level responses	p20
BADS	Rule shift cards	p51
	DEX	Score 20
Episodic memory		
Logical memory Ⅰ	Recall unit (Story A + B)	p20
(WMS-III)	Recall thematic (Story A+ B)	p20
Logical memory Ⅱ	Recall unit (Story A + B)	p30
(WMS-III)	Recall thematic (Story A + B)	p30
Word list Ⅰ (WMS-III)	Recall total score	p50
	Short-delay recall	p85
Word list Ⅱ (WMS-III)	Recall	p70
	Recognition	p85
Rey-osterrieth complex figure test	Recall	p50
Naming		
Boston naming test		p50
Praxis and visuo-constructive ability		
Rey-osterrieth complex figure test	Copy	p75
Gesture imitation		Normal
Complex sequencing		Normal

[1]It shows slight deficits in speed information processing, in planning as well as in attention to designated targets and to inhibit responses. FAS: Foreign Agricultural Service; WAIS-III: Wechsler Adult Intelligence Scale-III; WAIS: Wechsler Adult Intelligence Scale; BADS: Behavioural Assessment of the Dysexecutive Syndrome.

DAT SCAN showed an asymmetric decrease of the striatum tracer uptake more marked on the left side (Figure 3). Neuropsychological assessment did not show cognitive decline. However, it showed slight subcortical deficits (Table 1).

Case 2

A 76-year-old man, FMR1 gray-zone alleles carrier (expansion of 51 CGG) presented with a 3-year history of hand tremor and severe gait disorder. On examination he had mild postural tremor in both hands, mild rigidity more marked in the left side, lost of postural stability, severe tremor in a standing position, ataxia and freezing.

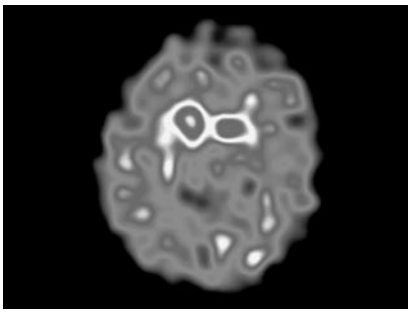

Figure 3 [^{123}I]FP-CIT DAT SCAN of the patient 1, it shows an asymmetric decrease of the striatum tracer uptake more marked on the left side.

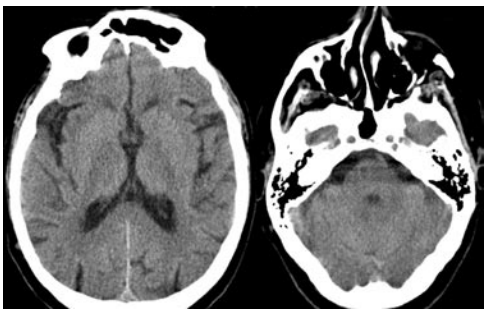

Figure 4 Cranial computed tomography of the patient 2, it does not show relevant findings.

He improved neither with 609 mg of levodopa nor with 1.5 mg of clonazepam. There were not cognitive decline.

Blood tests were normal. Cranial computed tomography and DAT SCAN were also normal (Figures 4 and 5). Electromyography corroborated high-frequency (14 Hz) tremor in a standing position in both legs which confirmed the diagnosis of orthostatic tremor.

DISCUSSION

Parkinsonism is often related to FXTAS, although most patients do not meet clinical criteria for PD[1,2]. Indeed, in parkinsonism related to FXTAS, response to levodopa is often poor[5,6], DAT SCAN is usually normal[5] and Single Photon Emission Computed Tomography with iodobenzamide has shown abnormal tracer uptake[6]. It leads to conclude that parkinsonism in FXTAS is developed by dysfunction beyond the presynaptic nigroestriatal level[5]. However, our first case, a parkinsonism with clinical features indistinguishable from PD, as similar cases previously reported[2], without intention tremor or ataxia and with both good response to levodopa and abnormal DAT SCAN suggests damage restricted to the presynaptic level. Thus, although the relationship between these "presynaptic parkinsonisms" and the FMR1 premutation could be casual, it is necessary to consider that the FMR1 premutation might cause two phenotypes of parkinsonism, such as a presynaptic phenotype, indistinguishable from PD, and a postsynaptic phenotype, associated with clinical features of FXTAS. In fact, neuropathological features related to the *FMR1* gene without Lewy bodies

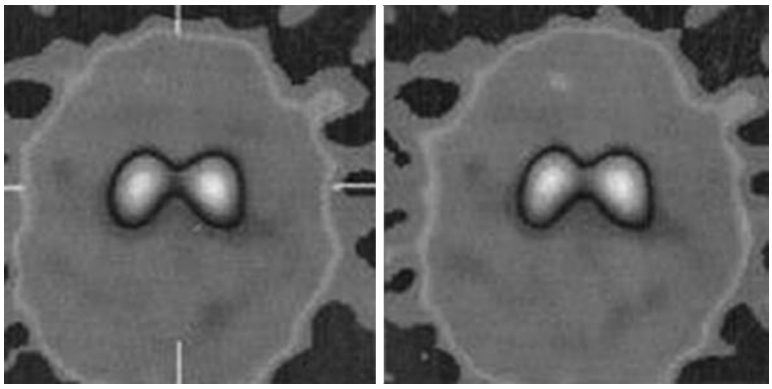

Figure 5 [^{123}I]FP-CIT DAT SCAN of the patient 2, it shows a symmetric and normal tracer uptake.

were found in a FMR1 premutation alleles carrier with clinical features of presynaptic parkinsonism[7] which supported the relationship between that presynaptic parkinsonism and the *FMR1* gene as well as ruled out a concomitant PD. How to explain it remains unclear, it could reflect either different ranges of severity or different stages of the same process or the coexistence of the FMR1 premutation with others genes associated with PD[8]. Thus, we suggest that FMR1 premutation should be considered in the differential diagnosis of PD, almost in those patients with family history of disorders related to the *FMR1* gene.

FMR1 gray zone alleles carriers were believed to have no abnormal neurological conditions. However, a recent report has suggested a relationship between FMR1 gray zone alleles carriers and FXTAS[3]. In this sense, our second case, presented with usual clinical features of FXTAS, such as parkinsonism, hand tremor and ataxia, supports the fact that FMR1 gray zone alleles carriers could develop FXTAS. Indeed, orthostatic tremor has not been described before in association with the *FMR1* gene. Thus, the presence of orthostatic tremor in our second patient expands the clinical spectrum of neurological disorders associated with the *FMR1* gene. Future research should validate findings on a larger group of patients.

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