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Case Report

A Case Report of Fragile X Premutation with Unusual Presentation

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Abstract

Objective: To report the unusual onset of fragile X-associated tremor/ataxia syndrome in a patient.

Clinical Case Report: A sixty-five-years old male patient with a history of progressive spastic paraparesis developed one-year later intention tremor and cerebellar ataxia. This neurological clinical status plus his daughter history of possible primary ovarian insufficiency and the discovery of bilateral and symmetrical high intensity signals in the cerebellar white matter at the base of middle cerebellar peduncles in cerebral magnetic resonance imaging guided to the diagnosis of fragile X-associated tremor/ataxia syndrome. This diagnosis was confirmed by genetic testing.

Conclusion: Fragile X-associated tremor/ataxia syndrome has a wide spectrum of neurological features, and spastic paraparesis may not only be one of them but also its initial manifestation like part of an unusual presentation. This case report shows the broad range of manifestations that has a disease like FXTAS, reason for what this disorder should be considered not only in the etiological diagnosis of a chronic cerebellar syndrome but also in others clinical pictures like a chronic spastic paraparesis.

Keywords: *Tremor; Ataxia; Spastic Paraparesis; Fragile X*

Introduction

Fragile X syndrome (FXS) is a genetic disease caused by the expansion of the CGG trinucleotide repeats, more than 200, in the promoter region of the fragile X mental retardation 1 (FMR1) gene, located at Xq27.3 [1]; it is considered the most common cause of inherited intellectual disability [2]. Healthy people have less than 45 CGG repeats, expansion to 46-54 repeats is considered the gray zone and individuals with 55-200 repeats are considered to have the premutation (PM) [3]. Carrier patients of the PM can develop conditions associated with fragile X; among there are fragile X-associated primary ovarian insufficiency (FXPOI) [4], fragile X-associated neuropsychiatric disorders (FXAND) [5] and fragile X-associated tremor/ataxia syndrome (FXTAS) [6].

FXTAS was first described in 2001 by Hagerman when he reported five elderly males who were carriers of the PM and presented with a progressive intention tremor, difficulty with ambulation, deficits in executive function and brain atrophy [7]. FXTAS mostly affects middle-aged and elderly men of 50 - 70 years old [8]. Intention tremor and cerebellar ataxia are its main motor features, but, this entity has got a high phenotypic variability, for that reason, some patients can exhibit dementia, neuropsychiatric problems, eye gaze abnormalities, other movement disorders, peripheral neuropathy, autonomy dysfunction, and others [3,8].

FXTAS can mimic many common neurodegenerative disorders such as Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), Alzheimer's disease (AD), essential tremor (ET), and spinocerebellar ataxias (SCAs) [3,8].

The diagnostic criteria for FXTAS were established in 2003 [9] and later revised in 2014 [10]. These diagnostic criteria include molecular, clinical, neuroradiological and neuropathological aspects and allow to establish the diagnostic categories of definite, probable and possible FXTAS [9,10].

This report shows the clinical case of an old male patient with a history of progressive spastic paraparesis who also developed intention tremor and cerebellar ataxia one year later. During the study of this individual bilateral cerebellar white matter hyperintensities located at the base of middle cerebellar peduncle (MCP) were found. For that reason, plus his daughter history of possible primary ovarian insufficiency, a genetic testing for FXTAS was performed and the diagnostic was confirmed.

The objective of this article is to report the unusual onset of fragile X-associated tremor/ataxia syndrome in a patient.

Clinical Case Report

A sixty-five-years-old male patient with history of arterial hypertension began with progressive gait problems due to stiffness and weakness of both legs since the age of sixty-three years. The patient also began to notice first tremor in both hands and later more gait difficulties that caused several falls in the last year. There is no family history of neurological diseases but daughter's patient suffers from irregular menstrual periods since the age of thirty-seven years. The patient denied urinary or bowel symptoms, erectile dysfunction, loss of smell, orthostatic intolerance, weight loss, steatorrhea or diarrhea, and sleep disorders; these last symptoms were corroborated by his wife.

The neurological physical exam displayed spastic-ataxic gait (hyperextension of knees, wide based stance, uncoordinated gait, and staggering from side to side), symmetrical muscular weakness in both lower limbs, more proximal that distal (Medical research council scale, 3/5 and 4/5 bilaterally), bilateral ankle and patellar hyperreflexia, bilateral unsustained ankle clonus, spasticity in both legs (Ashworth scale score, 2 bilaterally), dysmetria and dysdiadochokinesia in both upper limbs, symmetrical intention tremor in both arms, and asymmetrical (more right than left) postural tremor that involves wrist flexion-extension.

Neuropsychological evaluation, using Montreal Cognitive Assessment (MOCA) and Frontal Assessment Battery (FAB), was performed. The patient did not show global cognitive impairment (MOCA: 28/30 points) but executive function deficits (FAB: 13/18) was displayed by him.

Motor and sensory nerve conduction studies (NCSs) did not show signs of peripheral neuropathy.

A brain magnetic resonance imaging (MRI) was performed to this patient and bilateral and symmetrical high intensity signals in cerebellar white matter at the base of middle cerebellar peduncles in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images were observed (Figure 1). Also a cervical and thoracic spine MRI were carried out realized but no abnormalities were found.

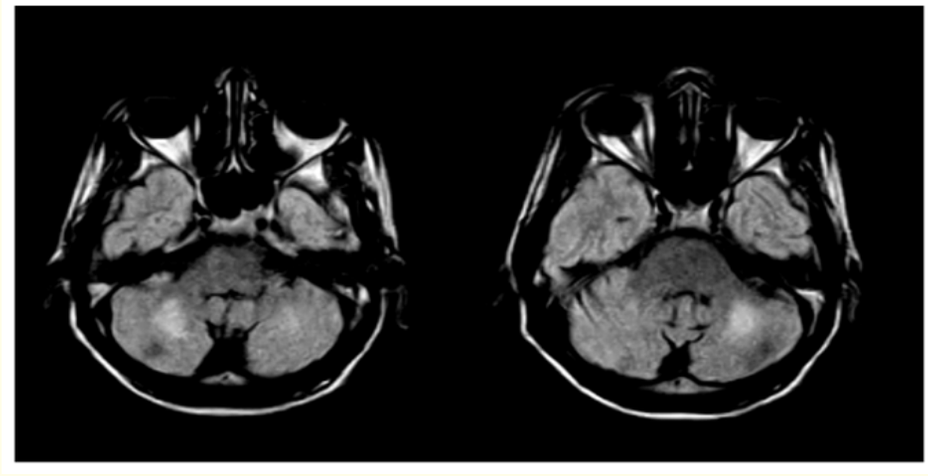

Figure 1: *Axial FLAIR images showing bilateral and symmetrical cerebellar white matter base of middle cerebellar peduncles.*

The hematologic, serum and chemical tests performed to this patient were normal (Table 1).

Variable			Patient's result	Reference range
Hematocrit (%)			41.0	40.0-50.0
Hemoglobin (g/dl)			14.1	12.0-15.0
White cells count (per mm^3)			6,000	4,500-11,000
Differential count (%)	Neutrophils		61	55-65
	Lymphocytes		35	25-40
	Monocytes		3	3-8
	Basophiles		0	0-1
	Eosinophils		1	1-5
Platelets (per mm^3)			259,000	150,000-350,000
Partial thromboplastin time (sec)			35	30.0-60.0
Prothrombin time (sec)			12	11.0-15.0
Glucose (mg/dl)			74	60-100
Creatinine (mg/dl)			1.1	0.6-1.5
Urea nitrogen (mg/dl)			16	8-25
Aspartate aminotransferase (U/liter)			14	9-32
Alanine aminotransferase (U/liter)			28	7-30
Protein (g/dl)		Total	6.7	6.0-8.3
		Albumin	3.8	3.3-5.5
Erythrocyte sedimentation rate (mm/hr)			7	1-20
C-reactive protein (mg/liter)			4.7	< 8.0
Antinuclear antibody			Negative	Negative
Antineutrophil cytoplasmic antibody			Negative	Negative
Serum complements (mg/dl)		C3	90	83-177
		C4	23	15-45
Cobalamin (pg/ml)			670	200-900
Folate (ng/ml)			13	2-20
α-tocopherol (µmol/l)			19	11.9-30
Thyroids hormones	T3 (ng/dl)		91	80-220
	T4 mg/dl		7.2	5.0-12.0
	TSH mIU/l		1.1	0.5-5.0

Table 1: *Results of hematologic, serum and chemical tests.*

Any abnormalities were found during the analysis of Cerebrospinal Fluid (CSF) (Table 2).

Variable	Patient's result	Reference range
Opening pressure (cm of water)	16	< 25
Color	Colorless	Colorless
Turbidity	Clear	Clear
Xanthochromia	None	None
Red cells (per mm^3)	0	0-10
White cells (per mm^3)	0	< 5
Glucose (mg/dl)	55	40-80
Protein (mg/dl)	27	15-45
Oligoclonal bands	0	0
IgG index	0,5	< 0,6
Gram's stain	No organism seen	No organism seen
Acid-fast smear	No organism seen	No organism seen
Chinese ink stain	No organism seen	No organism seen
Culture (routine, viral, mycobacterial, and fungal)	Sterile	Sterile

Table 2: *Analysis of CSF.*

And screening of systemic cancer were performed to this patient and no abnormalities were discovered. Tumour markers [prostate specific antigen (PSA), human chorionic gonadotropin (hCG), carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9), and alpha-fetoprotein (AFP)], an abdominal ultrasound, a lymph nodes ultrasound and a chest X rays were the studies carried out like part of this screening.

Serological test for the diagnosis of infections like Human Immunodeficiency Virus (VIH) antibodies, Venereal Disease Research Laboratory (VDRL) test and Human T-lymphotropic Virus 1 (HTLV-1) antibodies were performed in blood and in CFS. All of them displayed normal results. By other hand serum cooper and antigliadin antibodies could not be performed to this patient because we did not have availability.

The clinical status of this patient, in which intention tremor and cerebellar ataxia were remarkable, plus the pathological finding of cerebral MRI and the history of her daughter with menstrual irregularities, which is a symptom that can be due to primary ovarian failure, allow us to think in the diagnosis of a FXTAS case. Of course, the absence of any other possible cause, like showed the results of laboratory investigations, provided more value to this presumptive diagnosis. For that reason, molecular diagnosis of an FMR1 gene mutation was performed to this patient and the result was 96 CGG repeats.

Physical therapy was initiated like part of treatment. Baclofen (30 mg per day), amantadine (300 mg per day) and primidone (500 mg per day) was prescribed for the control of spasticity, cerebellar ataxia and intention tremor respectively.

Discussion

FXTAS is a genetic disorder caused by an expanded CGG trinucleotide repeat located in the 5′ untranslated region of the FMR1 gene [11]. It is considered one of the phenotypes of PM [6].

It mostly affects middle-aged and elderly men of fifty to seventy years old [8]. The patient reported the beginning of neurological symptoms at the age of sixty-three-years.

The core features of FXTAS are intention tremor and cerebellar ataxia [3]. Early sixties are the peak age of onset of tremor in the PM carriers, approximately 2 years prior to the onset of ataxia [3,12]. This tremor is typically an intention tremor but may also be a postural tremor [12]. Head tremor, and voice tremor are found in 10% of patients with FXTAS [3,8,12]. A resting tremor can be observed in 13 - 26% of individuals with FXTAS and it typically co-occurs with other categories of tremor [3,8,12]. Cerebellar ataxia is characterized by gait ataxia with difficulty in performing tandem gait, taking a longer time to turn, and increased gait variability like the initial signs [3], it is also characterized by limb ataxia due to the finding of dysmetria, dysdiadochokinesia, and rebound on physical exam [3]. The initial complaint was not an intention tremor or cerebellar ataxia in this case, however, both manifestations appeared one year later and they acquired a great relevancy like part of the clinical status. It is also important to notice that the reported patient exhibited postural tremor too.

FXTAS has a wide spectrum of neurological features like dementia, executive function deficits, neuropsychiatric problems, sleep problems, eye gaze abnormalities, parkinsonism, dystonia, peripheral neuropathy, autonomy dysfunction, vestibular symptoms, hearing impairment and olfactory symptoms [3,8,12]. This patient showed executive function deficits as exposed on his neuropsychological assessment.

In the last years, some reports have been published with the aim of to stand out the atypical onset of FXTAS patients [8,13,14]. This atypical onset is based in the initial presentation of neurological features like spastic paraparesis [13,14] and orthostatic tremor [8] in patients who develop with the time the classic clinical status of FXTAS. The patient reported in this paper had an onset characterized by spastic paraparesis with a gradual course and one year later he began to experience the typical neurological manifestations of male patients with the PM.

Two other conditions that carrier patients of the PM can develop are FXPOI [4] and FXAND [5]. Menstrual irregularities and difficulties to get pregnant characterize FXPOI [4]. Patient's daughter's patient had been suffering from irregular menstrual periods since a relative younger age, reason why a presumptive diagnosis of FXPOI was considered.

FXTAS has distinct features on MRI [3,8,10,15]. MRI examination of these patients reveals an abnormal brain pattern that allows classifying this entity as a white matter disease due to the presence of supratentorial and infratentorial white matter lesions [3]. Bilateral ponto-cerebellar white matter lesions are one of the most frequents radiological features [3,8], and bilateral hyperintensities of the MCP, on T2-weighted MR or FLAIR images, that's known like the MCP sign, is the hallmark of FXTAS [9]. The MCP sign is found in 58 - 82% of males and 13% of females with FXTAS [3,15] and it can also be seen in some carriers without remarkable neurological symptoms [15]. Hyperintensities of the subcortical and periventricular white matters and the splenium of corpus callosum can also be seen in FXTAS patients but these radiological findings are not pathognomonic of this entity [3,15]. Brain atrophy has been described in several studies. Atrophy can be found in the entire cerebrum and cerebellum, particularly in the dorsomedial frontal-parietal regions, insula, medial temporal regions, thalamus, and striatum [3,9]. Ventricular enlargement is also present in the later stages of FXTAS as well as thinning of the corpus [16]. MRI of the current patient showed bilateral and symmetrical hyperintensities of cerebellar white matter at the base of middle cerebellar peduncles in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, and this radiological finding is congruent with the MCP sign. Other abnormalities were not found during this radiological study.

FXTAS can mimic many common neurodegenerative disorders such as PD, MSA, PSP, AD, ET, and SCAs [3,8]. The atypical presentation of this particular patient made us consider other diagnoses beyond the diseases previously mentioned. For that reason, we performed a

group of laboratory exams directed to find infectious, metabolic, autoimmune or paraneoplastic disorders that could explain all manifestations of our patient. The possibility of an acquired disorder was role out because any of these exams played abnormalities. The majority of the previously mentioned neurodegenerative disorders was easily role out when we consider the features displayed and not displayed by this patient.

The diagnosis of FXTAS is established according to its diagnostic criteria [9,10]. In the reported patient the evidence of the two major clinical criteria and the major neuroradiological criteria plus the discover of FMR1 mutation, 96 CGG repeats, allowed to establish the definite diagnosis. Although some comparative analyses on FXTAS patients did not reveal an effect of the size of the CGG repeats on certain aspects of the disease, such as onset of signs, life expectancy and severity of neuropsychiatry symptoms [21], several recent studies produced strong evidence of the effect of the size of the CGG repeats on FXTAS manifestations, including cognitive and executive skills, motor dysfunctions, brain volumetric measures, initial age of symptoms and number of cells with intranuclear inclusions [15,21].

The expansion of the CGG trinucleotide repeats in the promoter region of the fragile X mental retardation 1 (FMR1) gene, located at Xq27.3, is the cause of FXS and FXTAS [3]. FMR1 gene codes for the fragile X mental retardation protein (FMRP), and FMRP is an RNA binding protein that is involved in several processes including neuronal plasticity and functioning of neuronal networks [17,18]. Three different molecular mechanisms have been implicated in the pathophysiology of FXTAS: the production of toxic FMRpolyG by repeat associated non-AUG (RAN) translation, the RNAs and protein sequestration into intranuclear inclusions, and the DNA damage caused by R-loop formation [3].

One of the neuropathological hallmarks of FXTAS is the presence of eosinophilic intranuclear inclusions in the central and peripheral nervous systems [19]. These eosinophilic inclusions have shown to stain positive for ubiquitin, lamin A/C and various heat-shock proteins, and their biochemical composition is very heterogeneous with no single predominant protein species [3,19]. By other hand postmortem FXTAS brains present with iron accumulation in brain capillaries and parenchyma, as well as in the choroid plexus [20] and macroscopic pathological findings reveal severe white matter disease, cortical atrophy, mild to severe ventriculomegaly, and spongiosis of cerebellar white matter [3,19].

Up to now, there is no targeted treatment to reverse this disease [3,19]. Principles of management include maintaining a healthy lifestyle and treatment of coexisting conditions to prevent rapid progression of FXTAS [19]. Hypertension, obstructive sleep apnea, hypothyroidism, neuropsychiatric disorders, and vitamin deficiencies can potentiate cognitive decline [3]. Also, concomitant treatable causes of cerebellar ataxia should be considered in cases with significant gait symptoms; this typically include testing liver and renal function, a-tocopherol, cooper, thyroid function, and autoimmune and paraneoplastic disorders [22]. Some medications may help symptoms of FXTAS such as a selective serotonin reuptake inhibitor (SSRI) for depression or anxiety, a beta blocker, primidone or levetiracetam for tremor, and gabapentin, pregabalin or duloxetine for neuropathic pain, amantadine for cerebellar ataxia [3,19]. In the reported patient the pharmacological treatment was based in the utilization of primidone for amelioration of tremor, amantadine for the relive of cerebellar ataxia and baclofen for the treatment of spasticity. Physical therapy was, of course, also indicated and the promoting of a healthy lifestyle was part of the treatment too.

Conclusion

FXTAS has a wide spectrum of neurological features, and spastic paraparesis may not only be one of them but also its initial manifestation like part of an unusual presentation. This case report shows the broad range of manifestations that has a disease like FXTAS, reason for what this disorder should be considered not only in the etiological diagnosis of a chronic cerebellar syndrome but also in others clinical pictures like a chronic spastic paraparesis.

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