Neurología. 2010;**25(4)**:222-227

NEUROLOGÍA

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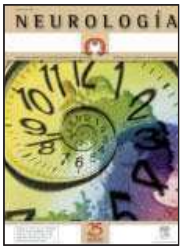

ORIGINAL ARTICLE

Neurological signs in the adult with fragile-X premutation

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Received on 22nd June 2009; accepted on 11th January 2010

KEYWORDS
Fragile X premutation;
Tremor/ataxia syndrome;
Parkinsonism;
Cognitive deficit

Abstract
Introduction: Fragile X syndrome is an inherited form of mental retardation. It results from an abnormally expanded number of trinucleotide CGG repeats. Some grandfathers of these children become forgetful, have frequent falls and other neurological problems. Researchers have found a connection between fragile X syndrome and the neurological symptoms in elderly men. This resulted in the recognition of a syndrome originally referred to as "intention tremor, parkinsonism and generalised brain atrophy in carriers of a fragile X premutation". This premutation is also associated with premature ovarian failure.
Methodology: This paper reviews the literature on the neurological signs of fragile X premutation.
Conclusions: Fragile X premutation is a risk for movement disorders and cognitive dysfunction and it should be considered in patients with a family history of mental retardation or autism, and particularly in those females with premature ovarian failure.

PALABRAS CLAVE
Premutación X frágil;
Síndrome temblor/ataxia;
Parkinsonismo;
Deterioro cognitivo

Manifestaciones neurológicas en el adulto con premutación X frágil

Resumen
Introducción: El síndrome X frágil es una forma de retraso mental heredado. Es consecuencia de una expansión anormal del número de repeticiones del trinucleótido CGG. Algunos abuelos de estos niños llegan a ser olvidadizos, tienen frecuentes caídas y sufren otros problemas neurológicos. Los investigadores han encontrado una conexión entre el síndrome X frágil y los síntomas neurológicos de los ancianos. Esto ha llevado a reconocer un síndrome inicialmente denominado "temblor intencional, parkinsonismo y atrofia cerebral generalizada en portadores de premutación X frágil". Al mismo tiempo, en las mujeres, la premutación se ha asociado a fallo ovárico prematuro.

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Metodología: Este artículo revisa la bibliografía acerca de las manifestaciones neurológicas de la premutación X frágil.
Conclusiones: La premutación X frágil supone un riesgo de sufrir trastornos del movimiento y disfunciones cognitivas y debe considerarse en pacientes con una historia familiar de retraso mental o autismo y, particularmente, en mujeres con fallo ovárico prematuro.

Introduction

Fragile X syndrome (FXS) is the most common cause of inherited mental retardation and is associated with a very characteristic physical and behavioural phenotype[1]. Due to its connection to the X chromosome, the prevalence among men (1:3,600) is higher than among women (1:8,000)[2].

As it is a childhood syndrome, it has been given little attention in adult neurology. However, late-onset neurological symptoms in relatives of children with FXS (that is, in carriers of the disease so far asymptomatic) have been described in recent decades.

The syndrome is caused by an unstable expansion of repetitions of the cytosine-guanine-guanine (CGG) triplet in the *FMR1* gene (*Fragile X Mental Retardation 1 gene*) on chromosome X (Xq27.3)[1]. In the so-called full mutation (MCX), which causes fragile X syndrome, more than 200 CGG repeats are identified, which are abnormally methylated, blocking the production of the *FMR1* gene protein (FMRP)[1]. In the healthy population, it is possible to find between 5 and 44 polymorphic repeats of CGG. Expansions of between 55 and 200 CGG repeats have non-methylated versions of the *FMR1* gene that result in FMRP values that are normal or near normality[3]. This interval of CGG repeats is called fragile X premutation (FXP) and is present in women and men who show no signs of FXS, but who can transmit the disorder. There is a "grey zone" between 45 and 54 CGG repeats, which behaves in an unstable manner during transmission, but which could expand and become MCX in 2 generations[4]. The transition from FXP to MCX occurs exclusively by maternal transmission, possibly during oogenesis. The risk of transition seems to depend entirely on the size of the expansion[5,6], and the role of AGG interruptions in the CGG sequence is currently being questioned[7]. Genomic deletions have also been described as a less common cause of FXS[8].

The prevalence of FXP among men is lower (1:813)[9] than among women (1:100)[10].

Pathogenesis and neuropathology

The FMRP protein is involved in the union, stability, transport and transcription of RNA with facial, skeletal, cardiovascular, endocrine and, especially, nervous system implications[11], where it intervenes in the regulation and transmission of information in the synapse through inhibition mechanisms[12]. A deficit or decrease of FMRP leads to an overexpression of cytoskeletal proteins, with particular relevance in the structure and plasticity of synapses and glutamate receptor 5, involved in the regulation of neuronal network excitability[13].

Histological studies on MCX have identified dendritic spines with immature morphology[14] and the formation of neuronal polyribosome aggregates[15] in relation to a decrease in size of the posterior cerebellar vermis[16], the caudate nucleus[14] and the hippocampus[17].

At first it was thought that FXP had little or no effect on *FMR1* expression and was therefore not associated with phenotypic manifestations. Subsequently, a decrease in FMRP production[18] and elevated *FMR1* concentrations in mRNA have been shown in subjects with FXP, indicating a low efficiency of the *FMR1*[19] gene and a cytotoxic effect[20] caused by inducing intranuclear accumulation of abnormal material in neurons and glial cells[21]. Inclusion bodies are distributed throughout the cortex and brainstem, with the highest density in the hippocampus and frontal cortex[22], but have also been identified in the suprarenal and mesenteric ganglion cells and in the posterior root and paraspinal sympathetic ganglia[23]. The inclusions are positive for ubiquitin, negative for polyglutamine, tau and synuclein; they are also related to the degradation of as yet unknown proteins[3]. A correlation between the number of inclusions and that of CGG repeats has been noted in FXP, and this could become a powerful predictor of neuropathological involvement[24-26]. By contrast, patients with MCX do not have intranuclear inclusion bodies[27]. More recently, researchers have identified perinuclear alpha-crystallin B-chain aggregates, which could be related to a predisposition towards neuroimmunological disease[28].

A loss of Purkinje cells, gliosis and involvement of the cerebral and cerebellar white matter with a pattern other than vascular, and spongiosis, particularly in the middle cerebellar peduncles, have also been noted[29] (table 1).

In short, the same gene has two opposite expressions: inactivity in MCX, which causes a deficit of FMRP and produces a neuro-developmental disorder, or hyperactivity in FXP, which induces excess mRNA with cytotoxic consequences and determines a neurodegenerative condition[30,31].

Clinical manifestations

The first descriptions of neurological symptoms in FXP carrier patients involved grandparents of children diagnosed with FXS and indicated cognitive impairment, tremors and impaired gait[29]. Gradually, further neurological symptoms associated with FXP have been collected. This has led to the definition of a separate clinical entity, currently known as

Table 1 Neuropathological findings in fragile X premutation

Significant affectation of cerebral white matter, with a pattern other than vascular, and spongiosis, predominantly in the middle cerebellar peduncles
Affectation of astrocytes with bulging by inclusions
Intranuclear inclusions in the brain and spinal cord

fragile X-associated tremor / ataxia syndrome (FXTAS)[29], which bears a certain correlation with FMRP values and years passed[32].

The clinical manifestations of FXP do not appear to be limited to FXTAS; a higher incidence of aggressiveness, alcohol and drug abuse, anxiety, obsessive-compulsive disorders[33] and learning problems[34] have also been reported. Some of the minor physical features characteristic of FXS have also been described: facial features, prominent ears, joint hyperflexibility, etc.[35] Likewise, there is evidence of a behavioural and neuropsychological phenotype associated with FXP in adults (without the clinical manifestations of FXTAS), which is, as yet, not well defined[36].

Initially, no deficit in neurodevelopment has been observed in children with FXP[37]. Subsequently, some relationship between FMRP values and mental retardation and/or autism has been identified, suggesting a spectrum of clinical severity related to the deficit of this protein[35,38], with a risk of cognitive and behavioural condition[39]. In fact, compared with healthy controls, children with FXP have a higher incidence of neuro-developmental delay, attention deficit, behavioural problems, anxiety and autistic disorders[40,41].

For a certain time, it was considered that women with FXP had no clinical symptoms. It was later noted that nearly 20% suffered premature ovarian failure[42], a distinctive phenotype with minor physical traits of FXS[35] and a higher incidence of anxiety and depression symptoms[43]. Premature ovarian failure does not occur in women with MCX, indicating that it is related to the toxicity of high *FMR1* levels in mRNA, present almost exclusively in FXP[8]. However, studies on women with FXP have the problem of sample heterogeneity due to the great variability of ratios of *FMR1* gene activation.

Fragile X-associated tremor / ataxia syndrome

Initially, FXTAS was defined as a pattern of progressive intentional tremor, cerebellar ataxia and cognitive impairment in males with late-onset (50-60 years old) FXP[29] and a prevalence that increased with age[44].

Subsequently, other clinical manifestations have been documented, including Parkinsonism, peripheral neuropathy, vegetative dysfunction, proximal weakness in lower extremities, behavioural disorders and dementia[45-48]. Cases of FXTAS have also been described in women, although fewer in number and with less severe phenotypes[22], which is explained by the presence of a second normal allele and by random X inactivation[49].

In 2006, Hall et al.[50] systematised the main clinical features of FXTAS and these were subsequently corroborated by other authors[51,52]. Most cases have abnormal gait (95%), tremor (80%), Parkinsonism (57%) and neuropathy in the lower extremities (60%).

Gait difficulties are mainly due to cerebellar ataxia exacerbated by Parkinsonism and/or peripheral neuropathy. The cerebellar condition also causes postural alterations, dysmetria and dysarthria.

Tremor is usually intentional (3-5Hz), but takes place during rest in 10% and is mixed in 30% It usually begins in the dominant hand and becomes bilateral after a few years. The severity of the tremor contrasts with the lightness of other symptoms.

Parkinsonism is expressed as moderate bradykinesia, mild rigidity in the upper extremities and resting tremor which, in some cases, is indistinguishable from idiopathic Parkinsonism[53].

Neuropathy is manifested by proximal leg weakness, hypoesthesia in middle leg (sometimes with cramps or burning), abolition of osteotendinous reflexes and moderate reduction of conduction velocity. An inverse correlation between conduction velocity and *FMR1* values has been found in FXP, with and without FXTAS[54].

Vegetative dysfunction usually presents as a loss of sphincter control (53%) and impotence (80%). Dementia occurs in 20% of cases, typically associated with agitation, aggressiveness, disinhibition and depression, thus describing a fronto-subcortical pattern[47].

The first manifestation is normally tremor and it poses a differential diagnosis[55-57]. Ataxia, Parkinsonism, peripheral neuropathy and cognitive impairment usually emerge gradually. In the later stages, the disorder can have the clinical and neuroimaging features of cerebellar type multiple system atrophy[58].

In a 12-year longitudinal study in patients with FXTAS, the number of CGG repeats was not associated with progression of motor or cognitive impairment[59]. However, a direct correlation between the size of the CGG repeats and the severity of motor deficits has been observed in males, while it was limited to the degree of ataxia in females[60]. Nevertheless, a recent study[61] associated small expansions of the CGG repeat with Parkinsonism. Moreover, only 40% of individuals with FXTAS have a family history of Parkinson's disease, dementia or non-specified degenerative disorders, which indicates sporadic forms of mutation or incomplete penetrance[62].

In FXTAS, cerebral magnetic resonance imaging (MRI) has identified changes in the white matter (prefrontal and cerebellar) and a reduction in the volume of the inferior

Table 2 Criteria for diagnosis of fragile X-associated tremor/ataxia syndrome

Criteria	Major	Minor
Radiological (magnetic resonance)	Lesions of the middle cerebellar peduncles. Brainstem lesions	Generalised atrophy (moderate-severe). White matter lesions
Clinical	Intentional tremor. Gait ataxia	Parkinsonism. Executive dysfunction. Loss of short-term memory (moderate-severe)

Table 3 Diagnostic probability of fragile X-associated tremor / ataxia syndrome

Diagnostic	Criteria: inclusion of 55-200 CGG repeats
Safe	1 major radiological sign+1 major clinical symptom or astrocytic inclusions
Probable	1 major radiological sign+1 minor clinical symptom or 2 major clinical symptoms
Possible	1 minor radiological sign+1 major clinical symptom

temporal cortex, amygdala, hippocampus and cerebellum[63]. There is in usually an increased T2 signal in the middle cerebellar peduncles and adjacent white matter, which has value as a diagnostic criterion[44]. More discrete changes have been identified in women with FXTAS than in men, but with the same pattern[64]. There is no correlation between the size of CGG repeats and cerebellar volume, increased ventricular size and white matter hyperintensity on MRI[25,65].

In 2004, the group of Jacquemont[44] proposed diagnostic criteria for FXTAS that would allow it to be differentiated from other movement disorders (tables 2 and 3), which were consolidated as a diagnostic guide through subsequent multidisciplinary studies[66,67]. Using these criteria, FXTAS prevalence in males over 50 years would be 1/3,000[44]. In different patient samples with essential tremor, sporadic progressive cerebellar ataxia, multiple system atrophy and atypical Parkinsonism without family history of FXS, no cases of FXP were identified[55,68-70]. Therefore, in adult males with late onset of ataxia, action tremor, Parkinsonism, cognitive impairment or neuropathy, the genetic study of FMR1 is only justified if there is a family history of mental retardation or autistic spectrum disorders[53,71] or if the MRI is indicative[72]. It is also justified in women with this background and some of the identified late-onset clinical manifestations, especially when they have suffered premature ovarian failure[64].

Some authors consider the *FMR1* study indicated in the differential diagnosis of spinocerebellar ataxias in male adults[69,73-75], particularly in oligosymptomatic cases showing an accentuation of the clinical signs and symptoms[76]. This possibility has also been noted in women diagnosed with multiple sclerosis with premature ovarian failure and atypical or torpid clinical course[77]. In our environment, Rodriguez-Revenga et al.[78] have pointed out the need to keep this entity in mind during the differential diagnosis of Huntington's disease.

In conclusion, in patients with clinical evolution of tremor and/or ataxia and/or atypical Parkinsonism and/or cognitive or behavioural conditions, we must always review the family history, looking for not only similar cases, but also cases of mental retardation, autism spectrum disorders and/or early menopause.

Conclusions

The extensive research conducted in the last decade has shown the dynamic nature of fragile X genotype and phenotype during a lifespan. However, further clinical and neuropathological studies are required to define its nosological implications better.

FXP is associated with a wide spectrum of clinical manifestations, especially neurological, in the so-called FXTAS, but also includes some neuropsychological deficits and specific neuropsychiatric symptoms.

With the current knowledge about FXP, it is necessary to bear this entity in mind with certain neurological manifestations in adults and it is also necessary to always inquire about a history of early menopause and/or FXS. Likewise, it is important to ensure efficient detection of fragile X syndrome in childhood which, in turn, will facilitate early identification of FXP in other family members.

Conflict of interests

The authors declare no conflict of interests.

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