REVIEW ARTICLE

Fragile X syndrome: clinical presentation, pathology and treatment

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Abstract

Fragile X syndrome is the monogenetic condition that produces more cases of autism and intellectual disability. The repetition of CGG triplets (> 200) and their methylation entail the silencing of the FMR1 gene. The FMRP protein (product of the FMR1 gene) interacts with ribosomes by controlling the translation of specific messengers, and its loss causes alterations in synaptic connectivity. Screening for fragile X syndrome is performed by polymerase chain reaction. Current recommendation of the American Academy of Pediatrics is to test individuals with intellectual disability, global developmental retardation or with a family history of presence of the mutation or pre-mutation. Hispanic countries such as Colombia, Chile and Spain report high prevalence of fragile X syndrome and have created fragile X national associations or corporations that seek to bring patients closer to available diagnostic and treatment networks.

KEY WORDS: *Fragile X syndrome. FMR1 gene. FMRP protein.*

Síndrome X frágil: presentación clínica, patología y tratamiento

Resumen

El síndrome X frágil es la condición monogenética que produce más casos de autismo y de discapacidad intelectual. La repetición de tripletes CGG (> 200) y su metilación conllevan el silenciamiento del gen FMR1. La proteína FMRP (producto del gen FMR1) interacciona con los ribosomas, controlando la traducción de mensajeros específicos y su pérdida produce alteraciones de la conectividad sináptica. El tamizaje de síndrome X frágil se realiza por reacción en cadena de la polimerasa. La recomendación actual de la Academia Americana de Pediatría es realizar pruebas a quienes presenten discapacidad intelectual, retraso global del desarrollo o antecedentes familiares de afección por la mutación o premutación. Países hispanos como Colombia, Chile y España reportan altas prevalencias de síndrome X frágil y han creado asociaciones o corporaciones nacionales de X frágil que buscan acercar a los pacientes a redes disponibles de diagnóstico y tratamiento.

PALABRAS CLAVE: *Síndrome X frágil. Gen FMR1. Proteína FMRP.*

Introduction

Fragile X syndrome (FXS) is a non-Mendelian nucleotide repeat disorder. FXS is due to the loss of function of the fragile x mental retardation 1 (*FMR1*) gene. The *FMR1* gene is found in chromosome Xq27.3 and encodes the FMRP protein, whose function is to control the translation of specific messengers. The repetition of CGG triplets (> 200 repeats) and methylation of the promoter entail silencing of the gene. However, the biological mechanism responsible for

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the presence of FXS is not fully elucidated. Approximately 30 % of girls and 90 % of boys affected with the full mutation have intellectual disability and 60 % of boys are diagnosed with autism spectrum disorders (ASD). Anxiety disorders occur in between 70 and 80 % of individuals with FXS.

FXS most accepted prevalence is approximately one in 5000 males and one in 4000 to 8000 females. However, there is still no global consensus due to the complexity of molecular diagnosis and the variety of clinical presentations in those who are not severely affected.[1] Much higher prevalence rates have been reported in Spain[2] and Colombia, where a genetic conglomerate with the highest prevalence of the syndrome so far was recently reported,[3] whereas an almost non-existent prevalence is reported in China, where the lack of research and clinical specialization in neurodevelopmental areas are speculated to be the main causes of the diagnostic sparsity of the syndrome.

Fragile X syndrome biological bases

The exact biological mechanism responsible for the occurrence of FXS is not known; however, it is known to lie in the ability of the FMRP protein to bind to RNA and proteins. Specifically, FMRP binds to ribosomes and is present in synaptic compartments, where it controls the translation of specific messengers. The loss of FMRP causes synaptic connectivity alterations in neurons, which result in FXS specific symptoms. These synaptic connectivity alterations are clearly observed in the brain as a decrease in the amount of dendrites and spines in the neurons of patients with FXS.

The lack of FMRP in neurons leads to glutamate receptors, both metabotropic ($mGluR_5$) and ionotropic (AMPA and NMDA), exacerbated expression.[4] γ-aminobutyric acid (GABA) and GABA receptors synthesis, degradation and transport proteins are also reduced.[5] The mechanisms whereby these changes in neurotransmitter systems affect the morphology of dendrites and spines in neurons is not exactly known, but they are suspected to be related. The role of the FMRP protein in glial cells is less known, but in FXS, the FMRP protein is known to regulate the translation of $mGluR_5$ in astrocytes[6] and the production of myelin in oligodendrocytes.[7] During prenatal development, radial glial cells contain FMRP, which intervenes in messenger RNA active transport along the glial fiber.[8] A change in any of these mechanisms can contribute to the development of cognitive disorders in patients with FXS.

FMRP has been associated with ion channel regulation. FMRP binds to the C-terminus of potassium-activated Slack channels. Slack channels' activation contributes to the activation patterns of a wide variety of neurons, suggesting that the alterations observed in FXS may be generated by altered activity patterns.[9] In turn, FMRP can also regulate the release of neurotransmitters through modulation of the action potential via large-conductance calcium-activated potassium channels (BK channels).[10]

The presence of a small fraction of FMRP in the cell nucleus indicates that said protein may have previously unrecognized functions. In fact, several studies have unveiled functions related to DNA expression and genomic function, such as DNA stabilization, DNA epigenetic regulation, nuclear RNA regulation and response to DNA damage.[11]

The amyloid β precursor protein (APP) has also been associated with FXS, through an $mGluR_5$ receptor-dependent mechanism. APP is processed by secretases that produce amyloid β (Aβ), a peptide that is predominant in senile plaques in Alzheimer's disease.[12]

Clinical presentation

Individuals affected with the *FMR1* gene full mutation have special phenotypic features that include an elongated face, large and prominent ears, joint hypermobility and macroorchidism.[13] More than 90 % of affected children have developmental delay and approximately 50-60 % are diagnosed with ASD.[14] During the course of their lives, both males and females show behavioral alterations commonly associated with the syndrome, usually of onset during childhood: anxiety and attention deficit and hyperactivity disorder (ADHD) are the most prevalent, although compulsive disorders such as hyperphagia and aggressiveness are also common (Table 1). In addition to behavioral alterations and learning and social adaptation problems, 15 to 20 % of patients with FXS have seizures, which are more prevalent in those with autism; more than 30 % have obesity problems, sleep disturbances and some gastrointestinal dysfunction, including gastroesophageal reflux. Strabismus and recurrent otitis media are common problems during early childhood.

The phenotype has some variants. Males are most commonly affected with the mutation; females have a phenotype that is attenuated by the activation index of the second unaffected X chromosome. More than 70 % of affected females have a low IQ, although this is considered average in comparison with the general

Table 1. Clinical characteristics

	Clinical characteristics	Prevalence
Physical	Long and narrow face Macrocephaly Prominent ears Prominent jaw Flat feet Macroorchidism Joint hypermobility	83 % more common in adults 50-81 % 75 % 80 % in adults 29-69 % 95 % since adolescence 50-70 % more common in boys
Psychological/psychiatric	ADHD ASD Anxiety Aggressiveness	80 % boys and 40 % girls 50-60 % boys and 20 % girls 58-86 % 40 % boys and 10-15 % girls
Developmental	Intellectual disability Language deficit	85 % boys and 25-30 % girls 100 % boys and 60-75 % girls
Other	Strabismus Otitis Gastrointestinal problems Obesity Seizures	8-30 % 50-75 % in childhood 30 % 30-60 % 15-20 %

Adapted from reference 14. ADHD = attention deficit and hyperactivity disorder, ASD = autism spectrum disorder.

population and in a lower proportion in comparison with males who have language problems.[13] The second variant are mosaics, which have some cell lines with the full mutation and others within the premutation range, which exposes them to the risk of suffering from the problems inherent to premutation such as tremor/ataxia syndrome (FXTAS);[15,16] or some cell lines with methylation and, therefore, with the silenced gene, and others without methylation, and in this case those affected also have a lower degree of cognitive compromise.[17]

In addition to the commonly recognized phenotypic characteristics, affected individuals have connective tissue anomalies of variable presentation, which are attributed to the fact that FMRP regulates essential components of the extracellular matrix. In addition to the most common musculoskeletal alterations, such as hyperextension of the metacarpophalangeal joints, flat feet and scoliosis, alterations in the cardiovascular and genitourinary systems have been described.[18]

Magnetic resonance imaging (MRI) of the brain of patients with FXS show that the brain is usually larger than normal and with an increase in the size of the lateral ventricles. The cerebellar vermis exhibits hypoplasia, one of the most representative features, which can be accompanied by a reduction of the entire cerebellum and alterations of the cerebellar peduncles. In addition, the caudate nucleus, especially the head, is larger, mainly in males. The hippocampus is also enlarged in young patients. In contrast, the insula and the amygdala are smaller. In addition, the uncinate fasciculus also exhibits white matter alterations.[13]

Interaction between FXS, autism and attention deficit and hyperactivity disorder

There is a close relationship between the presence of FXS, ASD and ADHD. Approximately 2 % of all cases diagnosed with autism spectrum disorders (ASD) are attributable to FXS, whereas more than 60 % of children with FXS are diagnosed with ADHD, ASD or both. FXS is the main genetic known cause of ASD; however, only 20 % of autism cases are recognized as the result of monogenic mutations, and only 2 to 6 % are due to *FMR1* gene mutation. Individuals affected by both morbidities, as it occurs in 50 to 60 % of boys and 20 % of girls with FXS, have more severe involvement of both cognitive and language deficits and behavioral problems.[19] Controlled clinical trials have demonstrated that, although FXS and ASD share psychiatric symptoms, affected individuals do not respond with the same efficacy to specific treatments,[20,21] which suggests that the same symptoms are originated by different mechanisms.

Diagnosis

Approximate age at FXS diagnosis is 36 months,[22] despite the fact that most parents report identifying some type of neurodevelopmental delay during the first year of life. Screening of high-risk populations can be carried out with polymerase chain reaction (PCR), a test of relatively low cost that requires a single drop of blood. The method uses a chimeric primer that

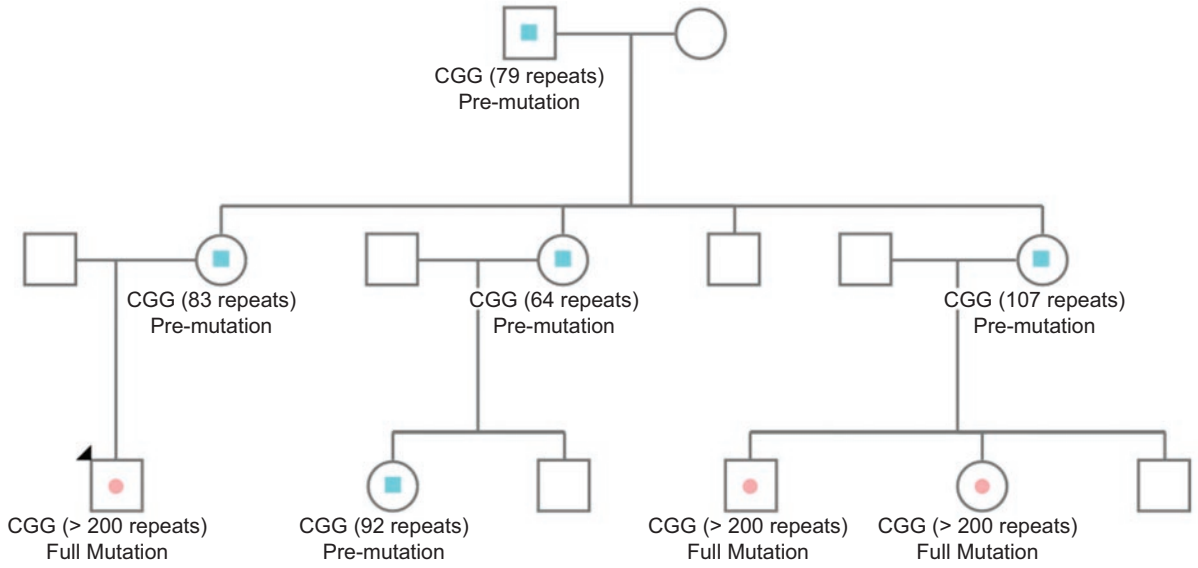

Figure 1. *Family tree. When establishing the molecular diagnosis, diagnostic cascade testing of all members of the immediate family is suggested. The male carrying the first-generation pre-mutation passes the pre-mutation to 100 % of his daughters, while his sons will not be carriers of the pre-mutation or the full mutation. The sons and daughters of women in the second generation have a 50 % likelihood of having the pre-mutation or the full mutation. Only females with the pre-mutation have the capability to expand the full mutation to both their male and female children and they have the capability to develop FXS, as well as those affected in third generation.*

Table 2. Fragile X syndrome clinical checklist

Characteristic	Score	
	1	2
Skin soft and velvety on the palms with redundancy of skin on the dorsum of hand		X
Flat feet		X
Large and prominent ears		X
Plantar crease	X	
Macroorchidism*	X	
Family history of intellectual disability	X	
Autistic behavior	X	
Total	4	6

*Males after puberty. The highest score is 10 points for males after puberty and nine for males prior to puberty or females. In patients with a score higher than 5, FXS molecular diagnosis should be considered. Adapted from reference 27.

randomly targets within the CGG enlarged region in the *FMR1* gene.[23] This method has been successfully used in several population-based studies.[2,3] The confirmatory diagnostic test is Southern Blot. Tejada made a thorough evaluation of the advantages and controversies of FXS prevention using prenatal diagnosis.[24] In 2017, Riley and Wheeler described the problems for postnatal screening to be established in the United States.[25] The American Academy of Pediatrics current recommendation is to carry out genetic testing in children with intellectual disabilities or global developmental delay.[26] If a new FXS case is found, diagnostic cascade testing should be performed in all members of the immediate family, in order to identify carriers of the premutation that have the potential to expand the full mutation to their offspring (Figure 1). Recently, Lubala et al. carried out a meta-analysis where 10 screening studies were included and a clinical score was proposed for the seven most specific features of FXS; this list takes into consideration the differences, especially the facial ones, which can be found in different ethnic groups. This clinical tool is of utmost importance in areas where not all individuals affected with intellectual disability or ASD can undergo genetic testing due to limitations in available resources (Table 2).[27]

Diagnosis in Hispanic countries

Despite the recommendation to carry out genetic tests in children with intellectual disabilities or global developmental delay and in those whose families are affected, these tests are not practiced in numerous Hispanic countries. Genetic diagnostic tests are available and several countries in Latin America have reported studies on the prevalence of FXS; however, determining the true prevalence of genetic disorders is difficult because in numerous Hispanic nations there is no official national registry. Countries such as Chile, Brazil, Colombia, Argentina, Peru and Spain have raised awareness on the

Table 3. Medications with efficacy in the treatment of fragile X syndrome

Medication	Maximum dose/day	Common adverse effects
Metformin	1000 mg < 50 kg 2000 mg > 50 kg	Nausea, diarrhea, headache, weight loss
Sertraline	2.5 to 5.0 mg children from 2 to 6 years 10 to 100 mg children older than 6 years and adolescents	Diarrhea, appetite loss, hyperhidrosis, tremor
Minocycline	25 mg < 25 kg 50 mg 25-45 kg 100 mg > 45 kg	Nausea, diarrhea, headache, dizziness, appetite loss, tooth and oral cavity discoloration, rash
Lovastatin	40 mg	Weakness, gastrointestinal symptoms, muscle pain/ tenderness/weakness, dizziness, headache, irritability
Acamprosate	1332 mg < 50 kg 1998 mg > 50 kg	Irritability, depressive symptoms, increased repetitive behavior, gastrointestinal symptoms including diarrhea and constipation

Adapted from references[21,29,33,38].

need for better screening and diagnostic processes for prevalent genetic diseases, including FXS, to be implemented. In addition, there are economic, political and social barriers the neurogenetic field has to face, mainly in developing countries.[2,3] Currently, FXS diagnosis is mainly based on phenotypic findings, with the possibility of genetic testing upon recommendation of the specialist. In many cases, tests are not performed due to their high cost, because they are not covered by health insurances and, in other cases, due to the limited availability of certified laboratories to perform DNA analyses in blood samples.

Treatment

There is no cure for FXS, and treatment is therefore limited to the control of associated symptoms. Currently, the research lines focus on developing effective treatments for the different psychiatric and cognitive problems suffered by those affected (Table 3). In 2017, Gantois et al. investigated the efficacy of metformin as a modulator of the mGluR/mTORC1-ERK cascade in animal models of FXS, and reported an improvement in social and cognitive behavior, as well as in morphological (dendritic spine dysgenesis and macroorchidism) and electrophysiological abnormalities (long-term depression).[28] These findings motivated the initiation of metformin treatment research in clinical practice. The first report showed benefit mainly in problematic behaviors such as irritability, aggressiveness and social evasion in adult patients with FXS, in addition to benefits in appetite and weight control in subjects with the Prader-Willi phenotype.[29] For this reason, current controlled studies both in the United States and Canada seek to determine the efficacy of metformin in the treatment for this syndrome.

Sertraline is a first-line medication for the management of depression and anxiety. It was studied for its potential benefit on language; however, it showed better results in motor and visual perceptual skills and social participation in FXS.[21]

Minocycline is also considered a beneficial treatment in FXS. It has been shown to reduce the levels of matrix metallopeptidase 9 (MMP-9),[30] a zinc-dependent endopeptidase responsible for regulating synaptic activity, which is critical for central nervous system development and plasticity.[31] Its inhibition is caused by its binding to FMRP, a protein that is absent in FXS. MMP-9 regulation problems are considered part of the pathophysiology not only of learning problems, but also of abnormalities found in the connective tissue.[18]

Acamprosate, an mGluR5 receptor antagonist, modified anxious behavior and locomotor tests in an FXS animal model[32] and demonstrated improvement in areas of social behavior and hyperactivity in pediatric patients with ASD and FXS.[33] It should be considered a beneficial medication for the management of patients with FXS and alcohol addiction problems.[34]

Studies of lovastatin treatment in FXS animal models postulate this medication as prophylactic treatment for epileptogenesis and suggest that it might improve sensory and cognitive functions.[35] Non-controlled clinical trials demonstrated good tolerance to the treatment, with few adverse effects, and reported benefits in both behavior and adaptive skills.[36] At the molecular level, changes in extracellular signal-regulated kinase (ERK) phosphorylation were shown to be related to clinical response to lovastatin.[37]

There are other medications that can improve neurobiological systems in FXS and that are not considered specific treatments for the syndrome, but that

help to control the most common psychiatric characteristics. These include stimulants (methylphenidate and amphetamines) and atomoxetine, which can improve symptoms of attention disorder and hyperactivity syndrome, usually in children older than five years; alpha adrenergic agonists (guanfacine or clonidine) can also be used in children younger than five years of age to calm hyperactivity. Clonidine is especially effective in improving sleep disorders, should there not be a good response to melatonin treatment. For the management of aggressiveness or mood disorders, antipsychotics (risperidone or aripiprazole) are adequate, but they can cause weight gain.

Conclusion

Individuals affected with FXS have intellectual disability, ASD and ADHD. Although there are many medications for the management of common comorbidities, there are no specific treatments. The goal of early treatment is to improve intellectual disability and communication and social interaction difficulties, which are characteristic of FXS. In addition, despite the recommendation to perform genetic testing in children with intellectual disabilities or global developmental delay, this is not carried out in many of the Latin American countries. It is of utmost importance for FXS analysis to be implemented in all Hispanic countries.

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Conflicts of interest

Randi J. Hagerman has received funds from Roche, Novartis, Neuren, Marinus and Alcobra to carry out therapeutic studies in patients with FXS. He has also consulted with Fulcrum and Zynerba about therapeutic studies in individuals with FXS. The other authors declare that they have no conflicts of interest.

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