

Psychiatric Aspects and Management of Fragile X Syndrome: Case of Siblings in Morocco

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Keywords

Fragile X syndrome, Behavioral disorder, Autism spectrum.

Introduction

Fragile X syndrome is a genetic abnormality of the X chromosome. It is considered the most frequent monogenic cause of the combination of autism spectrum disorder and intellectual development disorder.

Its prevalence is estimated at 1 in 5000 boys and 1 in 9000 girls in the general population. Clinically, its manifestations are not very specific and vary from one individual to another. This syndrome is more often diagnosed in boys than in girls, but it is highly likely that the prevalence in girls is underestimated because the symptoms are less obvious than in boys [1].

Fragile X syndrome is caused by mutations in the FMR1 gene located on the X gene, with the Xq27.3 locus coinciding with the folate-sensitive fragile site [2]. Today, molecular biology methods based on the study of FMR1 gene DNA have replaced the cytogenetic methods used, and make a major contribution to the diagnosis of the disease thanks to PCR.

The Fragile X mutation is the most common isolated genetic cause of autism spectrum disorders. It is present in 6% of boys with Fragile X syndrome. Individuals with Fragile X syndrome associated with autism spectrum disorder have impaired intellectual development and significant impairment in language and expressive skills, compared with subjects carrying Fragile X alone [3,4].

In this article, we report the clinical case of two brother and sister, both carriers of fragile X syndrome, whose diagnosis was made through psychiatric symptoms that dominated the clinical picture.

Case Report

This 26-year-old patient, the eldest of two siblings, was undergoing child psychiatric treatment for a behavioural disorder involving psychomotor instability and bizarre behavioural patterns, which had become increasingly disorganized as he grew older. Motor stereotypies were observed. Language acquisition was late, around the age of 5, and he presented difficulties in understanding and learning. His schooling was mediocre, and his parents had to stop him in the second year of primary school, later integrating him into a multidisciplinary center for people with special needs. He found it difficult to take part in all the activities the center offered, and refused to attend any of them afterwards. He was diagnosed with an intellectual development disorder comorbid with an autism spectrum disorder. During her medical consultations, numerous biological blood tests were carried out, showing no detectable abnormalities. However, around the age of puberty, her face became clearly dysmorphic, and dysarthria was noted, altering her speech, which is marked by incoherence and slurred speech. At the age of 16, he became violent and unmanageable by his family, adopting bizarre behaviors and attitudes marked by opposition even towards his parents. He was put on atypical antipsychotics, olanzapine 10mg/day, and his behavior improved markedly. The evolution of his clinical condition fluctuated, with bouts of irritability and impulsivity that did not lead to aggression, but did cause him multiple accidents in the home. This prompted

carbamazepine treatment at a dose of 200 mg then 400 mg/day. He is currently well stabilized on this treatment.

His sister came to a psychiatric consultation at the age of 34 for a psychological assessment as part of a pre-employment procedure. During the psychiatric interview, we noted that her childhood was marked by delayed psychomotor development and an intellectual disability with impaired adaptive functioning. Schooling was impossible, and she would have briefly attended a center for people with Down's syndrome. Her face was less dysmorphic than her brother's, and not at all suggestive of genetic disease, hence the delay in diagnosis. A genetic workup was ordered, and molecular analysis came back in favor of fragile X syndrome in this girl. There was no need to prescribe medication for her, but she was offered multidisciplinary care.

It's important to note that both siblings come from non-consanguineous marriages, and both parents have no physical or psychic symptoms that could point to genetic counseling for Fragile X syndrome. It should be noted that their mother had hyperthyroidism comorbid with Gougerot Sjogren's disease.

Discussion

Fragile X syndrome is the second most common cause of intellectual disability after trisomy 21, and the most frequent cause of hereditary intellectual disability, due to its highly specific mutational mechanism [5].

Fragile X results from a dynamic mutation by CGG triplet amplification in the regulatory region of the FMR1 gene, which occurs in two stages over the generations: unlike the general population, which usually has fewer than 55 CGG triplets, in families affected by fragile X, a grandfather or grandmother carries a premutation, i.e. a higher number of triplets, between 55 and 200, greatly increasing the instability of this structure, which will tend to amplify from generation to generation [6,7]. If it is carried by a male, he passes it on without amplification to all his daughters, who in turn pass on to 50% of their children a mutation that may remain as a premutation or be amplified to a full mutation (> 200 CGG) [8]. Full mutation causes methylation of the FMR1 gene, inhibiting its expression; it is the absence of synthesis of the FMRP protein (encoded by FMR1) that is responsible for the symptoms of fragile X. In girls, the clinical expression of the full mutation is extremely variable, probably related to the pattern of X chromosome inactivation in the brain. Individuals carrying the premutation do not have Fragile X syndrome, and therefore no intellectual impairment, but 20% of women have premature ovarian failure, and men are at risk of developing a neurodegenerative syndrome called Fragile X Tremor Ataxia Syndrome (FXTAS) [9-11].

In boys, the infant is sometimes hypotonic, but postural acquisitions are usually only slightly delayed. The young child presents a language delay, often with gaze avoidance and significant psychomotor agitation, which leads the parents to seek

help. The first diagnostic step is therefore to identify and confirm that the child has a delay in psychomotor development. To orient the etiological diagnosis of this developmental delay towards fragile X syndrome, several clinical signs can be identified: early on, ligament hyperlaxity with valgus feet and subluxation of the thumbs. Evocative morphological features often only appear in older children, and may not be present at all: wide, high forehead, sometimes macrocephaly, elongated face, long mandible, large ears, macro-orchidism (after puberty). Clinical signs in girls are often more attenuated, revealing themselves in learning difficulties or, more often, emotional disorders (anxiety, social withdrawal). Some girls may present with similar symptoms to boys. A family history of neurodevelopmental or psychiatric disorders may help to guide the diagnosis [12].

In our case, however, there is no family history of psychiatric or neuropsychiatric disorders. Genetic diagnosis requires a molecular biology study of the CGG trinucleotide expansion of the FMR1 gene (Southern Blot or commercial PCR kits for faster diagnosis and accurate estimation of premutation size). Diagnosis should always be followed by a genetic consultation with a geneticist or genetic counsellor [13]. Intellectual development disorders are usually of moderate to severe severity, and impact on the ability to understand new or complex information. This has a major impact on learning at school, and limits the ability to adapt to everyday situations in adulthood. Two-thirds of patients express themselves in sentences, often with pronunciation problems, perseveration and speech organization difficulties. Reading is possible for less than half of patients. Motor hyperactivity is very marked in young boys, and diminishes in adolescence. Poor working memory and attention problems severely impair learning. Anxiety and emotional regulation impair social interaction, with maladaptive behaviours (stereotypies, verbal automatisms, excessive arousal) [14]. Some patients present a genuine autism spectrum disorder, as in the case of the boy whose case is reported in this article. His sister, on the other hand, has an intellectual development disorder that falls within the framework of fragile X syndrome.

Consent

Informed consent was obtained from the mother of both patients in accordance with current regulations.

References

1. <https://www.chu-lyon.fr/syndrome-de-lx-fragile>
2. Bailey DB Jr, Raspa M, Bishop E, et al. No change in the age of diagnosis for fragile x syndrome: findings from a national parent survey. *Pediatrics*. 2009; 124: 527-533.
3. Cordeiro L, Ballinger E, Hagerman R, et al. Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: prevalence and characterization. *J Neurodev Disord*. 2011; 3: 57-67.
4. Sullivan K, Deborah Hatton, Julie Hammer, et al. ADHD symptoms in children with FXS. *Am J Med Genet A*. 2006; 140: 2275-2288.

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5. Irwin SA, Patel B, Idupulapati M, et al. Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: a quantitative examination. *Am J Med Genet.* 2001; 98: 161-167.
 6. Carrasco M. Informing members of families affected by fragile X syndrome of this diagnosis. *Rev Neurol.* 2001; 33: S37-S41.
 7. Tassone F. Newborn screening in fragile X syndrome: prevalence and allele distribution of the FMR1 gene. Paper presented at: American College of Medical Genetics Annual Clinical Genetics Meeting. 2012.
 8. Jacquemont S, Curie A, Portes V, et al. Epigenetic modification of the FMR1 gene in fragile X syndrome is associated with differential response to the mGluR5 antagonist AFQ056. *Sci Transl Med.* 2011; 3: 64ra61.
 9. Hall SS, Walter E, Sherman E, et al. The neural basis of auditory temporal discrimination in girls with fragile X syndrome. *J Neurodev Disord.* 2009; 1: 91-99
 10. Hallahan BP, Craig MC, Toal F, et al. In vivo brain anatomy of adult males with fragile X syndrome: an MRI study. *Neuroimage.* 2011; 54: 16-24.
 11. Harris SW, Hessel D, Goodlin-Jones B, et al. Autism profiles of males with fragile X syndrome. *Am J Ment Retard.* 2008; 113: 427-438.
 12. Hatton DD, Sideris J, Skinner M, et al. Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP. *Am J Med Genet A.* 2006; 140A: 1804-1813.
 13. Hatton DD, Wheeler A, Sideris J, et al. Developmental trajectories of young girls with fragile x syndrome. *Am J Intellect Dev Disabil.* 2009; 114: 161-171.
 14. Hazlett HC, Poe MD, Lightbody AA, et al. Teasing apart the heterogeneity of autism: same behavior, different brains in toddlers with fragile X syndrome and autism. *J Neurodev Disord.* 2009; 1: 81-90.
 15. Hazlett HC, Poe MD, Lightbody AA, et al. Trajectories of early brain volume development in fragile X syndrome and autism. *J Am Acad Child Adolesc Psychiatry.* 2012; 51: 921-933.