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Fragile X- associated Neuropsychiatric Disorders: A Case Report

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Abstract

Mutations in the Fragile X Mental Retardation 1 (*FMR1*) gene create a spectrum of developmental disorders in children in addition to neurodegenerative problems in older populations. Two types of mutations are recognized in the *FMR1* gene. The full mutation (>200 CGG repeats) in the *FMR1* gene leads to Fragile X Syndrome which is the most common inherited cause of intellectual disability and autism, while the premutation (55 to 200 CGG repeats) identified among carriers leads to a range of problems linked to elevated levels of the *FMR1* mRNA leading to mRNA toxicity and occasionally mildly deficient FMRP levels. Two disorders among premutation carriers have been recognized namely: the Fragile X-associated Primary Ovarian Insufficiency (FXPOI) and Fragile X-associated Tremor/Ataxia Syndrome (FXTAS). Recently, in order to recognize a group of associated disorders commonly found in premutation carriers and extensively reported in co-morbidities studies, a new distinctive name was proposed: Fragile X-associated Neuropsychiatric Disorders (FXAND). This paper will present a case report of a female premutation carrier who has encountered predominantly psychiatric problems, but also chronic pain and sleep disturbances consistent with FXAND.

Keywords

FMR1; Fragile X-associated Neuropsychiatric Disorders; FXAND; premutation carrier; anxiety; depression

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Introduction

Fragile X Syndrome is caused by the amplification of CGG repeats in the Fragile X Mental Retardation 1 (*FMR1*) gene. Mutations in the *FMR1* gene can lead to developmental disorders in children and to neurodegenerative problems in older populations. The full mutation (>200 CGG repeats) in the *FMR1* gene leads to Fragile X Syndrome (FXS) which is the most common inherited cause of intellectual disability and autism. The premutation (55 to 200 CGG repeats), which is found in approximately 1 in 200 women and 1 in 400 men [1], can also lead to problems that stem from elevated levels of the *FMR1* mRNA leading to mRNA toxicity, and occasionally mildly deficient FMRP levels [2]. A few associated disorders among premutation carriers have been previously named, including Fragile X-associated Primary Ovarian Insufficiency (FXPOI), a condition that occurs in an estimated 16 to 20% of carriers and characterized by menopause before 40 years old [3 4], as well as Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) which is diagnosed in about 16% of females and 40% of older male premutation carriers [5–7]. However, there have been increasing reports of female premutation carriers who present with a variety of neurologic, psychiatric, sleep and autoimmune conditions which has recently been called Fragile X-associated Neuropsychiatric Disorders (FXAND), a group of conditions, primarily neuropsychiatric in presentation, affecting approximately 50% of carriers [8]. This case report illustrates many of the conditions associated with FXAND in a woman with the premutation.

Materials and methods

This patient was evaluated as part of the Fragile X Treatment and Research Center located at the University of California Davis MIND Institute for management of Fragile X disorders. Detailed medical history, physical, and neurological examinations were done. The neurological examination was carried out by a medical doctor and included evaluating cranial nerve function, reflexes, muscle tone, rigidity, sensation, gait, coordination, and the presence of abnormal movements. The patient signed an IRB approved informed consent to have her case history published. Here, we describe the patient's medical history, neuropsychiatric symptoms, and findings on medical and neurological evaluations.

Molecular measures

CGG Repeat sizes and Activation ratio were determined using PCR amplification and Southern blot analysis gene according to the conditions described in Tassone et al. 2008 and Filipovic-Sadic (2010) [9, 10]. *FMR1* mRNA expression levels were determined by quantitative RT-PCR as detailed in Tassone et al. (2000) [2].

Case Report

This is the case of a 55-year-old woman, diagnosed as a premutation carrier with two alleles of 29 and 70 CGG repeats, an activation ratio of 0.62 (which express the percent of cell carrying the normal allele on the active X chromosome), and an *FMR1* mRNA expression level of 1.9 (0.04) fold higher compared to controls. She presented with longstanding

problems in anxiety, depression, inattention, chronic pain, and opioid use. Maternal and birth histories were unremarkable while developmental milestones were met within normal limits. Retrospectively, she reports experiencing anxiety and “panic attacks” in early childhood, as far back as 3 years old, and these have persisted well into adulthood. She initially performed well in school despite her dislike of reading. Attentional, organizational, and academic problems emerged in high school which led to poor grades and increased parent-child conflict, although no diagnosis or treatment was given at that time. These events, alongside living with a high-achieving sibling who was not a premutation carrier, exacerbated her anxiety and reportedly led to a negative self-image.

The patient took to drinking alcohol as an adolescent to ostensibly “self-medicate” her anxiety and stress that resulted from her poor self-image and her conflict with parents regarding her poor school performance. In her 20s, she was diagnosed with depression and anxiety, and prescribed fluoxetine, with beneficial effects. Bupropion Hcl was also given for her depression from 2000 to 2017 but it eventually stopped working even at a dose of 300 mg a day. Throughout her adult life she has continued to take 40 mg of fluoxetine per day.

The patient later experimented with street amphetamines which helped her deal with her symptoms of inattention. She was only recently diagnosed with attention-deficit/ hyperactivity disorder (ADHD) and currently takes Adderall 20 mg/d, a preparation of mixed amphetamine salts, which improves her attention and concentration.

Opioid abuse is also present, and this has been an intermittent problem for many years. The patient was first treated with hydrocodone after experiencing postoperative pain from a cesarean section delivery. This helped alleviate her pain and feelings of depression. Her hydrocodone use increased and became excessive after successive stressful events occurred including the death of her father, her son’s diagnosis of autism spectrum disorder (ASD), and her being diagnosed as a premutation carrier. She was treated for alcohol and opioid use in an outpatient program with temporary improvements but relapsed which resulted in her admission to an inpatient rehabilitation program. After one year, she relapsed again after her mother passed away. Currently, she reportedly limits her alcohol intake to 2 drinks a day and she uses hydrocodone 5mg three times a day. Whenever she stops taking hydrocodone, her depression symptoms become so severe that it triggers another relapse into hydrocodone use again.

She has been experiencing intermittent low back pain for about 20 years, which she believes might have been due to her involvement in gymnastics when she was younger. But in the last 2 years, she has been having chronic pain problems described as constant pain in her neck and shoulders, right arm, and trapezius muscles. There has been no history of surgery on her back. She was never diagnosed with fibromyalgia. A rheumatologist consultation was done several years ago and a blood test then revealed a positive ANA titer at 1:360.

The patient had “tics” in childhood described as chewing on her tongue and repetitively tapping on a table. These tics improved after puberty but reappeared following her stress about her mother’s passing. Her tics worsened further after her dosage of Adderall was increased to 30mg thus, the dose was kept at 20 mg.

She had one child, also carrier of the premutation. She never had symptoms associated to premature ovarian insufficiency and onset of menopause was at age 52. Movement-related concerns were reported at age 47 characterized by intermittent tremors while manipulating a computer mouse. Recently the tremors have improved in that she currently does not notice them. She does not report any symptoms indicative of ataxia although she has tripped a few times without falling down. Additional problems include numbness in her fingertips but not in her feet. She also experiences chronic fatigue which is alleviated by Adderall.

The patient has had vasovagal episodes when she was pregnant, and, more recently, she experienced orthostatic hypotension whenever she stood up quickly from a sitting position.

Cognitive issues have likewise been reported. The patient claims to have had memory problems including word retrieval difficulties that began originally at age 38 but have worsened in her 50s.

She reports past behaviors characterized as “manic behaviors”, which are consistent with the criteria for bipolar disorder in partial remission on the Structured Clinical Interview for the DSM-5 (SCID-5). The patient also has sleep problems because of racing thoughts but sleep improved with intake of trazodone 50 to 75 mg at night. She refused benzodiazepines to treat her sleep problems because of her concern that these could be addicting. She also reports frequent snoring but has not had a polysomnogram to diagnose sleep apnea.

She continues on fluoxetine 40 mg a day, Adderall 20 mg /day, trazodone 75 mg at bedtime and hydrocodone 5 mg three times a day. The patient has an exercise regimen of at least 4 hours per week and works as a personal trainer as she recognizes the importance of exercise for her physical and mental health.

The patient’s current SCID-5 evaluation documents subthreshold depression on fluoxetine, past poly-drug abuse, and meeting the DSM-5 criteria for social phobia and specific phobia for elevators.

On neurological exam, there were no obvious tremors with finger to nose touching. With positioning, there was a subclinical tremor in the right hand more than in the left hand, but it was very slight and there was no resting tremor. Vibration sense was normal in all extremities. Primitive reflexes were absent. On tandem walk, she had to leave some space in between both feet to maintain her balance while executing the motor task. She had an MRI that did not demonstrate any signs of atrophy and did not have the middle cerebellar peduncle sign, but did show slight white matter disease in the pons on the right hemisphere and in the insula. Her corpus callosum was without atrophy but with slight involvement of the splenium and hyperintensities on T2, representing white matter disease.

The patient does not meet diagnostic criteria for FXTAS; however, most of her symptoms involve neuropsychiatric problems, therefore putting her in the FXAND diagnostic category. See Table 1 for a summary of her medical history.

Discussion

Here, we present a case of an adult female premutation carrier with a lifelong history of anxiety and intermittent depression consistent with FXAND [8], but who does not meet the criteria for FXTAS [11,12]. Her case will add to the clinical data on FXAND, a recently described Fragile X-associated disorder.

FXAND is a proposed umbrella term that represents the neuropsychiatric conditions associated with Fragile X premutation carriers. It is not limited to one entity but includes various neuropsychiatric disorders. It primarily presents with neuropsychiatric symptoms in premutation carriers who do not have the clinical signs of FXTAS such as significant action tremor and/or cerebellar ataxia in addition to white matter disease on MRI and white matter hyperintensities in the middle cerebellar peduncles (MCP sign) [8,11,12] Neuropsychiatric problems in FXAND emerge before the neurological problems develop in FXTAS and onset is typically at an earlier age than FXTAS[8].

Due to the presence of a 70 CGG repeat allele, she was subsequently diagnosed as a premutation carrier. The relationship between CGG repeats and the prevalence of major depressive disorder is curvilinear. This means that the middle range of 70–100 repeats confers the greatest risk, while repeats on the lower-end and higher-end of the premutation range confer lower risks of psychiatric problems [13].

As a premutation carrier with major depression that meets the DSM 5 criteria, she is labelled as suffering from FXAND due to the association of depression with the premutation carrier status. She presented with a constellation of neuropsychiatric problems that is more in number and more severe than the usual patient with FXAND. The number of neuropsychiatric conditions present in this patient further strengthens the association of these disorders with the umbrella term FXAND seen in premutation carriers.

The neuropathological mechanisms that lead to neuropsychiatric disorders of FXAND are still unclear, although the mechanisms underlying FXTAS may shed some light into this. Problems associated with the premutation are related to the RNA toxicity because of elevated *FMR1*-mRNA. Neurons of premutation carriers are more vulnerable to environmental toxins [12] and more neural death is seen in cell cultures [14]. Ca++ dysregulation and elevated cytoplasmic Ca++ levels are also present in premutation neurons [15] which may be associated with the mitochondrial dysfunction that worsens at the onset of FXTAS [16,17]. Chronic DNA damage repair and the formation of FMRpolyG, a toxic protein, [18] are also related to the toxicity of the premutation that leads to the neurodegenerative process in FXTAS. Similar neuropathological mechanisms may be found in FXAND resulting in the dysfunction of neural systems responsible for behavior and emotion regulation.

A recent paper by Brown et al (2019) compared 17 male carriers without FXTAS to 17 age matched controls (ages 24 to 70) and found higher rates of psychopathology in the carriers than controls. In addition, the fMRI studies demonstrated remarkably lowered activation patterns to emotional stimuli compared to controls. These findings did not correlate or

change with age and they appear to represent life span problems of a neurodevelopmental origin perhaps related to neuronal connectivity deficits in carriers [19].

The patient reported experiencing anxiety from childhood and intermittent depression with multiple psychosocial stressors, consistent with findings about the trajectory and risk factors among premutation carriers. Higher rates of anxiety disorder are seen among *FMR1* premutation carriers compared to the general population. A lifetime prevalence for anxiety disorder in males with FXTAS is 50%, [20] and about 40 to 47% in premutation carriers without FXTAS [21]. These anxiety symptoms are present in adolescence in that approximately 50% of female premutation carriers would have met criteria for anxiety disorder before 18 years old [22]. Another study found higher rates when looking at both male and female carriers between 4 to 22 years old, with an estimated 70% fulfilling the criteria for at least one type of anxiety disorder compared to 9.8% in the general population. Psychosocial stresses further increase the risk of developing anxiety in carriers, including personal knowledge that one is a carrier [23], or parenting a child with problem behaviors [22]. In premutation carriers with FXTAS, anxiety is associated with progressive decline in cognitive abilities as neurodegenerative processes detrimentally impact on neural systems underpinning executive control and emotion regulation [20]. Depression is also frequently reported by carriers. The lifetime prevalence of major depressive disorder is approximately 40% among premutation carriers without FXTAS [20,24] and with FXTAS [20]. Male premutation carriers without FXTAS are more likely to rate themselves higher on depression scales relative to the normative population [20], with depressive symptoms predicted to worsen over time [25]. Depressive symptoms are also aggravated by chronic stressors including parenting a child with FXS [22] and comorbid medical conditions experienced by the carrier.

The patient had ADHD symptoms since childhood but was not diagnosed then - leading to her use of street amphetamines. ADHD is also common in premutation carriers [25] and it occurs in over 50% for carriers who present clinically. Attention deficits are also more common in premutation carriers than their non-carrier sibling - with more males (41%) demonstrating problems compared to females (18.5%) [26]. Hyperactivity may decline as body mass increases although inattentive symptoms may endure [27]. The *FMR1* mutation is a factor that could increase the risk for ADHD symptoms so this is included in FXAND [28].

Pain symptoms are often reported by adult premutation carriers. Fibromyalgia can occur in up to 40% of women with FXTAS [29]. The mechanism through which female premutation carriers develop fibromyalgia is likely to be via alteration of pain neurotransmission through pain dysregulation resulting from damaging effects of increased rates of transcription of expanded *FMR1* mRNA [30]. Both the ADHD symptoms and the pain symptoms have led to chronic substance abuse in this history and these problems have been mentioned in the literature regarding comorbidities in carriers [31,32]. They have also been included in diagnostic entities covered by FXAND. Additionally, higher rates of alcohol abuse have been documented in carriers, placing them at further risk for other neuropsychiatric comorbidities [33].

The patient reported reading difficulties due to inattention and experienced academic problems. However, she was never evaluated or given a diagnosis of a learning disorder. While not necessarily psychiatric, her learning problem was a major stressor during adolescence which could have increased her risk for anxiety and depression. Data about overall cognitive performance in premutation carriers are varied in that several studies showed normal overall cognitive abilities while other studies showed lower verbal IQ scores. Information about learning disorders is minimal beyond ADHD symptoms although arithmetic difficulties have been reported in females premutation carriers [34].

Chronic fatigue is common among carriers even before the onset of FXTAS, likely secondary to the mitochondrial dysfunction [35, 36]. Moreover, CNS volumetric changes occur throughout the lifetime in carriers particularly in the cerebellum and brainstem. Some of this patient's symptoms such as intermittent tremor are likely related to CNS changes. White matter disease in the CNS can occur even before the symptoms of FXTAS emerge [11] and this patient demonstrates white matter disease in the insula and in the splenium of the corpus callosum.

Sleep disturbances in premutation carriers are frequent and may be connected to their anxiety and depression. Sleep disturbances are related to the GABA deficits documented in premutation carriers [37] likely secondary to a mild FMRP deficit or to the RNA toxicity. Sleep disturbances may also be traced to the increased risk of sleep apnea in premutation carriers [38] which affects restorative sleep. This may play a role in the chronic fatigue they experience and predispose them to more attention and memory problems. Moreover, in regard to her son, although he does not have the full mutation, he has ASD which is seen in boys with the premutation [25]. This also comes under the diagnoses included in FXAND [8].

In sum, this is a case of a premutation carrier with complex neuropsychiatric symptoms consistent with FXAND which was not recognized early so she received delayed or inconsistent interventions. Her neuropsychiatric comorbidities, together with the challenges of parenting a child with ASD, the impact of her premutation diagnosis, and her experience of losing her parents, resulted in complex stresses that exacerbated the neurobiological vulnerabilities associated with the premutation.

Conclusion

This case report demonstrates that the neuropsychiatric symptoms associated with FXAND can be severe and lifelong, and require intensive therapy combined with pharmacotherapy. Individuals with the *FMR1* premutation are at an increased risk for developing anxiety, depression, ADHD, and substance abuse, and medical issues related to pain, chronic fatigue, sleep, and autoimmune problems. However, the association of these psychiatric problems with the premutation are not always acknowledged, resulting in missed diagnoses and suboptimal treatment. If more intensive interventions had been given to this patient in childhood, her lifelong history of neuropsychiatric issues, including substance abuse, probably could have been avoided.

The diagnosis of FXAND requires *FMR1* DNA testing. *FMR1* DNA testing to identify if one is a premutation carrier (55 to 200 CGG repeats), and a psychiatric evaluation to determine the presence of a neuropsychiatric disorder. These, along with genetic counseling, can guide treatment. Timely diagnosis is crucial due to the premutation carrier's increased risk of developing the comorbidities discussed here and having children with an *FMR1* mutation and accompanying neuropsychiatric conditions or developmental disabilities. Conversely, individuals presenting with mood or anxiety disorders and a family history of FXS, developmental delay, intellectual disability, or autism spectrum disorder should also be screened [33, 39].

Further investigations into the neurobiological and molecular underpinnings of FXAND are necessary to clarify the mechanisms leading to these neuropsychiatric conditions and to enhance treatments that alleviate these symptoms.

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Summary points

- FXAND is an umbrella term that represents the neuropsychiatric disorders associated with the
- *FMR1* premutation, which include anxiety, depression, obsessive compulsive disorder, chronic fatigue, insomnia, chronic pain and/or fibromyalgia.
- The neuropathological mechanisms leading to neuropsychiatric disorders of FXAND may be related to mitochondrial dysfunction secondary to RNA toxicity caused by elevated FMR1-mRNA. These are likely developmental and not neurodegenerative.
- FXAND can be mild or severe, and lifelong. Problems associated with FXAND usually respond well to counseling and pharmacotherapy.
- Anxiety, depression, and ADHD are commonly associated with the *FMR1* premutation.
- In premutation carriers with FXTAS, anxiety is common and is associated with an increase in hippocampal atrophy.
- Psychosocial stresses could increase the risk of developing anxiety in premutation carriers.
- Males premutation carriers often have ADHD and anxiety, while social deficits or autism are only occasionally seen.
- ADHD and chronic pain symptoms can potentially lead to chronic substance abuse in premutation carriers.

Table 1.

Summary of medical history

Diagnosis	Age of onset	Medication/dose per day
FMR1 premutation (70 CGG repeats)	N/A	
Anxiety	Chilldhood	Fluoxetine 40 mg (ongoing)
Social Phobia	Chilldhood	
Specific Phobia (elevators)	Chilldhood	
Depression	20s	Fluoxetine 40 mg (ongoing) Bupropion 300 mg (2010–2017)
Substance abuse	30s	Alcohol 2 drinks (ongoing) Hydrocodone 15 mg (ongoing)
Chronic Pain	30s	
ADHD	40s	Adderall 20 mg (ongoing)
Sleep disorder	50s	Trazodone 50 mg −75 mg (ongoing)
Memory deficit	50s	